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EPIDEMIC ENCEPHALITIS (ST. LOUIS TYPE) IN TOLEDO, OHIO

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Several outbreaks of epidemic encephalitis have occurred in the United States in recent years. The most severe epidemic was in St. Louis in the summer of 1933. Smaller outbreaks were reported in Paris, Ill., Kansas City, Kan., and St. Joseph, Mo. We wish to report observations made during an epidemic which occurred in Toledo, Ohio, during the summer of 1934. It is our purpose to demonstrate that the disease which occurred in Toledo is epidemiologically, clinically and pathologic-anatomically identical with the St. Louis type of encephalitis and the Japanese type of encephalitis (encephalitis B of Kaneko and Aoki [1]) and is not identical with lethargic encephalitis (Economo's disease). Of the fifty cases that occurred in Toledo (tables 1 and 2), clinical and pathologic examination was possible in two.

REPORT OF CASES

CASE 1.—*History.*—Henry L., aged 61, had headache, nausea and staggering gait on Aug. 29, 1934. On the following day the temperature was 103 F., and on the second day, 104 F. He became stuporous, but could be aroused with difficulty. On the third day the temperature returned to normal, but the stupor became deeper. Death occurred six days after the onset of symptoms. The only other clinical comment in the brief record was that no disturbances of the pulse and the respiration were noted.

The spinal fluid contained a pellicle, which, according to the examiner, "prevented an accurate estimation of cells." The protein and the sugar content were normal, cultures were sterile and stained smears showed no bacteria.

Necropsy.—There were cardiac hypertrophy, aortic stenosis and insufficiency, syphilitic aortitis and pleural adhesions. The brain was grossly normal except for sclerosis of the basal vessels.

The histologic changes consisted of: (1) perivascular cuffing (lymphocytes, occasional polymorphonuclear leukocytes and monocytes; fig. 1); (2) numerous peri-

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1. Kaneko, R., and Aoki, Y.: Ergeben. d. inn. Med. u. Kinderh. **34**:342, 1928.

vascular glial nodes (figs. 1 to 6); (3) atypical glial elements (Alzheimer type); (4) diffuse microglial and macroglial proliferation, and (5) neuronophagia.

1. The perivascular infiltrations were moderately severe, were not very numerous and were scattered throughout the nervous system (figs. 1 to 6). 2. The perivascular microglial nodes dominated the histologic picture. The microglia cells were either of the elongated (polyblastic) variety or round. Most of the nodes were compact formations built of microglia and contained neither leukocytes nor lymphocytes. 3. In severely inflamed areas of the brain stem, there were numerous large, slightly elongated glial nuclei, with scanty, or no, cytoplasm, which were intimately mixed with inflammatory elements. These were so-called atypical glial elements (Alzheimer). 4. Diffuse microglial and macroglial proliferation was encountered in the cortex and white matter of the hemispheres and the brain stem.

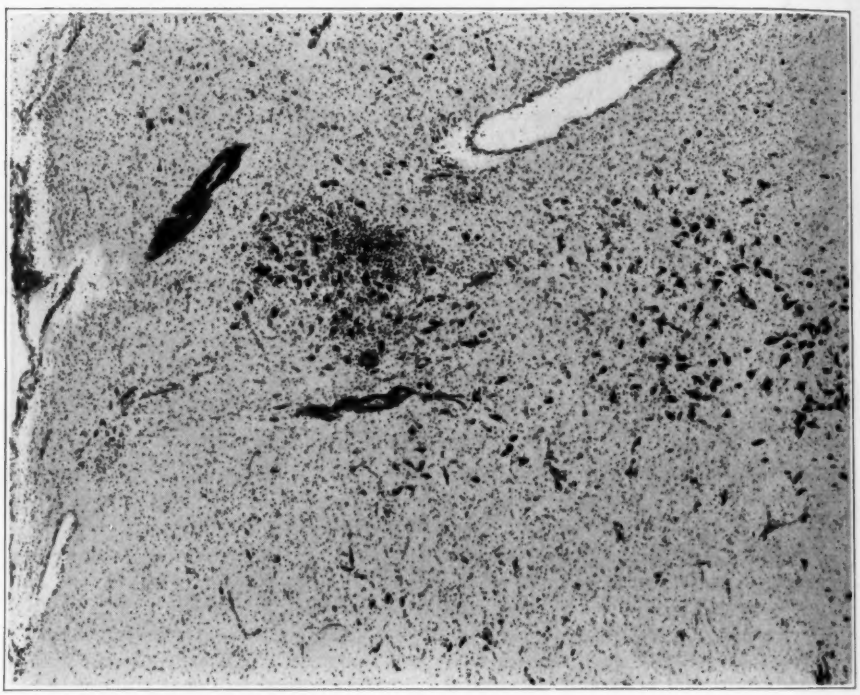

Fig. 1.—Section showing multiple tissue nodes and areas of perivascular infiltration in the substantia nigra. Nissl stain; Zeiss planar 20 mm.

5. Numerous examples of neuronophagia were present in the spinal cord and brain stem. The histologic picture was that of acute nonpurulent encephalitis.

Pattern of Inflammation: To simplify the study of the pattern, the brain was arbitrarily divided into several zones: 1. Midbrain. Severe inflammatory changes were present in (*a*) the central gray substance, (*b*) the substantia nigra (fig. 1), (*c*) the medial and lateral geniculate bodies (fig. 2), (*d*) the red nuclei, (*e*) the quadrigeminal bodies and (*f*) the cerebral peduncles.

2. Hypothalamus. In the nuclei of the walls and floor of the third ventricle there were mild inflammatory changes; the mamillary bodies were severely involved.

3. Basal Ganglia. The subthalamic bodies, the thalamus, the pallidum, the putamen, the caudate nucleus, the internal capsules, the claustrum and the external capsules were severely inflamed.

Fig. 2.—Section showing the corpus geniculatum laterale, with numerous tissue nodes. Nissl stain; Zeiss planar 50 mm.

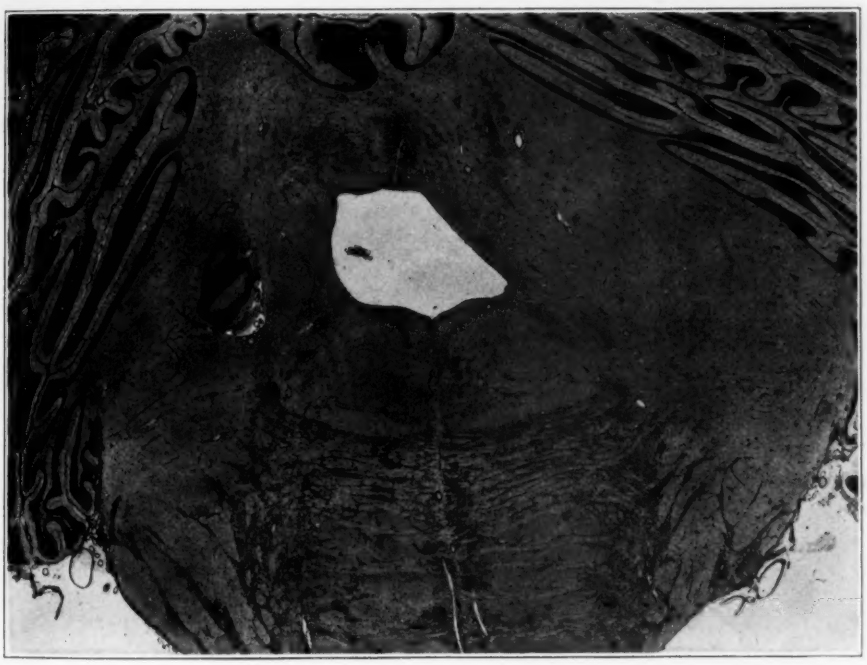

Fig. 3.—Section of the pons, showing multiple tissue nodes and perivascular infiltrations in both the basilar and the dorsal part, the white matter of the cerebellum and the corpora restiforme. Nissl stain; Zeiss planar 75 mm.

4. Medulla. The nuclei of all cranial nerves, the reticular substance and the olives were severely affected.

5. Pons. Severe inflammatory changes were evenly distributed over the dorsal and basilar parts (fig. 3).

6. Cerebral Cortex. The entire cortex contained numerous microglial nodes and scattered areas of perivascular infiltration. The cyto-architecture was not affected and the neurons showed only slight nonspecific changes (fig. 4).

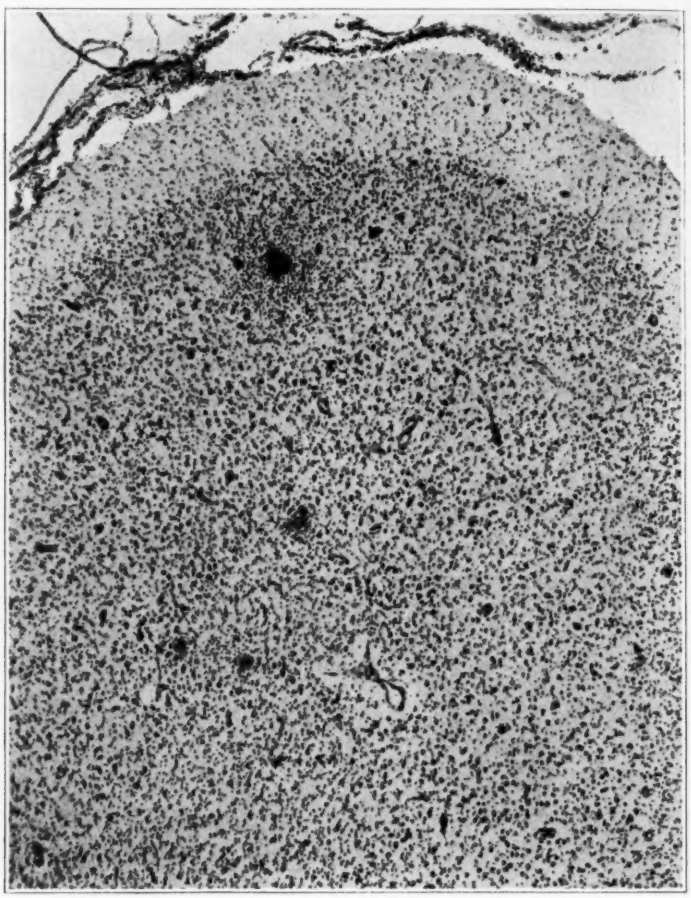

Fig. 4.—Section of the cortex, showing numerous tissue nodes and scattered perivascular and distinct meningeal infiltration. Nissl stain; Zeiss planar 20 mm.

7. Cerebral White Matter. This contained countless inflammatory foci in both the superficial and the deep layer (fig. 5).

8. Cerebellum. The cerebellar cortex, the white matter and the large gray nuclei were evenly and severely involved.

9. Spinal Cord. Outspoken inflammatory changes were present in the anterior horns, and there were scattered lesions in the posterior and lateral horns and in the white matter (fig. 6).

10. Meninges. There was a mild nonpurulent inflammation.

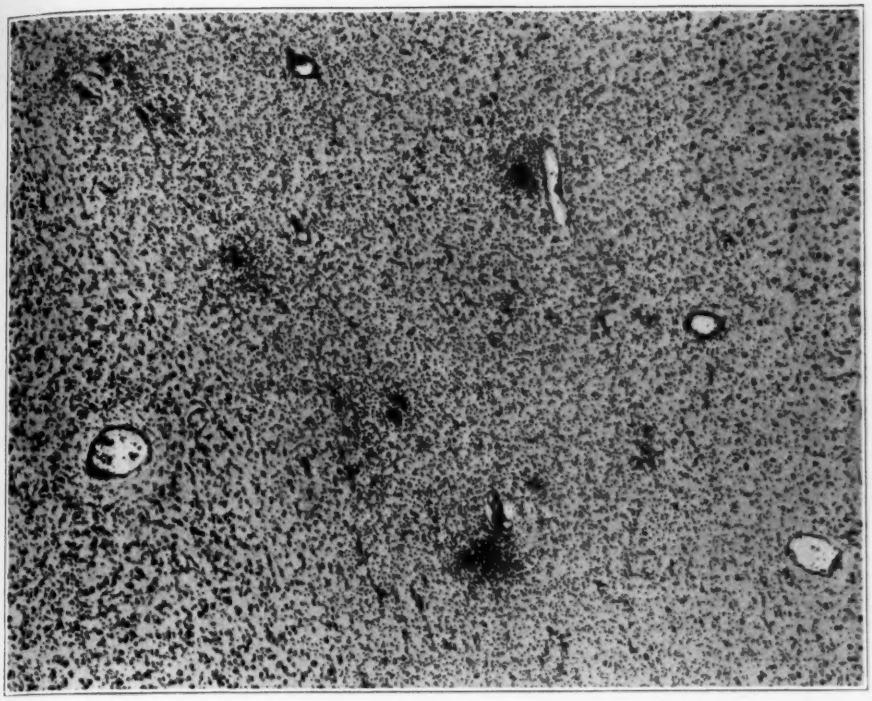

Fig. 5.—Section showing multiple tissue nodes and perivascular infiltration of the cerebral white matter. Nissl stain; Zeiss planar 20 mm.

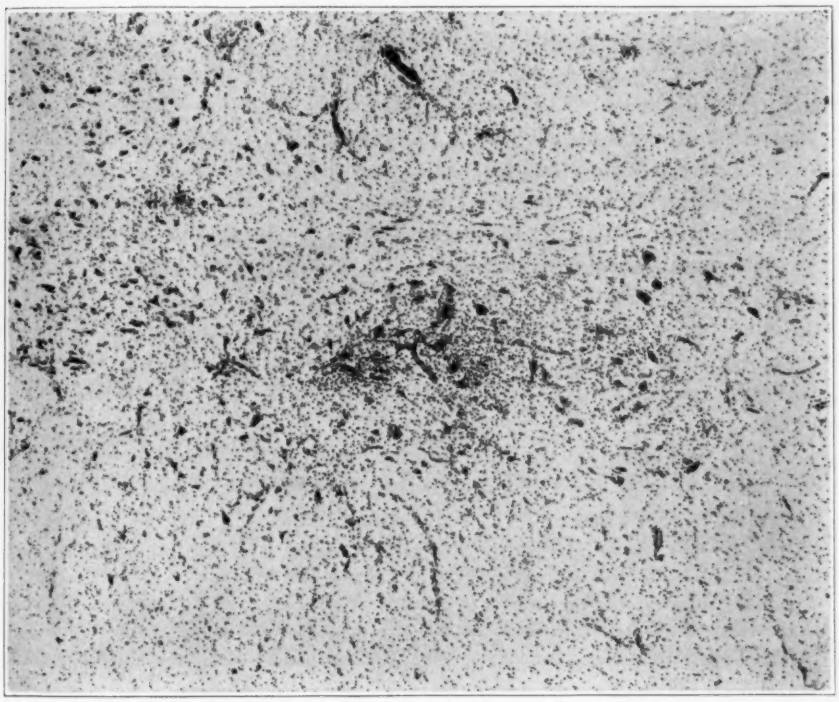

Fig. 6.—Section of an anterior horn of the thoracic segment of the spinal cord, with outspoken signs of acute inflammation. Nissl stain; Zeiss planar 20 mm.

Summary.—The inflammation involved the central nervous system diffusely, without preference for any region and without definite pattern.

CASE 2.—Laura C., aged 64, was admitted to the Flower Hospital on Aug. 24, 1934, in coma. The neck was rigid, and the upper extremities were spastic. The reflexes were exaggerated, and there was twitching of the muscles of the face and body. There was urinary retention followed by incontinence. The pupils were round, irregular and equal and reacted to light. The temperature was 106.2 F. The pulse was irregular, the rate ranging between 95 and 120; the respiratory rate varied between 20 and 40. Examination of the lungs revealed râles on both sides. Ecchymotic spots were noted on the knees. On August 21 the upper extremities became flaccid, but the neck remained rigid. Death occurred on August 26, four days after the onset of symptoms.

Laboratory Findings.—The spinal fluid was under pressure of 16 mm. of mercury, was clear and showed 410 lymphocytes, a normal globulin content (?) and a sugar content of 90 mg. per hundred cubic centimeters. Cultures were sterile, and smears gave negative results. The colloidal gold curve was 0012342210. The Wassermann reaction was ±. Examination of the blood revealed a hemoglobin content of 80 per cent, red cells 4,200,000 and white cells 21,050, with a differential count of polymorphonuclear leukocytes 14 per cent, segmented forms 66 per cent, lymphocytes 16 per cent and large monocytes 4 per cent.

Necropsy.—There was generalized arteriosclerosis of the organs of the body. Grossly the brain was normal except for sclerosis of the basal vessels.

The histologic changes corresponded in every respect with those in case 1, but the distribution of inflammation varied, in that the cortex and the white matter of the hemispheres were much less involved.

COMMENT

Histologic Picture and Distribution of the Inflammation in the St. Louis, Toledo and Japanese Types of Encephalitis.—American and Japanese authors (McCordock, Collier and Gray,[2] Weil,[3] Kaneko and Aoki [1]) have reported the presence of perivascular infiltration, numerous glial nodes, a diffuse microglial response, neuronophagia, degeneration of the neurons and mild meningitis. The Japanese authors observed in some cases small brown areas of softening in the basal ganglia, brain stem, pons and medulla, apparently produced by the disintegration of the glial nodes. Histopathologically, the epidemic encephaltis observed in Toledo was identical with that observed in St. Louis and, with the exception of the occurrence of areas of softening, with that observed in Japan.

The distribution of the inflammation as described by American and Japanese authors corresponded with that observed in the cases in Toledo. There was involvement of: (1) the spinal cord; (2) the medulla; (3) the pons; (4) the cerebellum; (5) the midbrain; (6) the hypothalamus;

2. McCordock, H. A.; Collier, W., and Gray, S. H.: The Pathologic Changes of the St. Louis Type of Acute Encephalitis, J. A. M. A. **103**:822 (Sept. 15) 1934.

3. Weil, A.: Histopathology of the Central Nervous System in Epidemic Encephalitis (St. Louis Epidemic), Arch. Neurol. & Psychiat. **31**:1139 (June) 1934.

(7) the basal ganglia; (8) the white matter of the hemispheres; (9) the cortex, and (10) the meninges. Severe inflammation was regularly observed in the brain stem, the basal ganglia and the white matter of the hemispheres. The cortex was involved in some cases and was spared in others. Of the two cases reported here, the cortex was severely involved in one and moderately in the other.

Histologic differentiation of the Toledo and the St. Louis encephalitis from lethargic encephalitis (Economo) is possible. The points of difference are: 1. In the St. Louis, Toledo and Japanese encephalitis the dorsal and basilar parts of the pons are regularly and severely involved (Kaneko and Aoki [1]); in lethargic encephalitis the inflammation is restricted to the dorsal part of the pons (Spatz [4]). 2. The entire width of the medulla is regularly involved in the St. Louis, Toledo and Japanese encephalitis, while in lethargic encephalitis the inflammatory changes are restricted to the nuclei of the cranial nerves and the reticular substance. The olives are frequently spared. 3. The cortex and the white matter of the cerebellum are regularly and diffusely inflamed in the St. Louis, Toledo and Japanese encephalitis and are usually spared in lethargic encephalitis, in which the changes are restricted to the dentate nucleus. 4. In the St. Louis, Toledo and Japanese encephalitis the inflammation in the midbrain is evenly distributed, while in lethargic encephalitis the red nuclei and peduncles are mostly spared. 5. The basal ganglia (caudatum, putamen, pallidum and thalamus) are regularly and severely affected in the St. Louis, Toledo and Japanese encephalitis, while in lethargic encephalitis the inflammation is mild or absent in these areas. 6. The cortex and the white matter of the hemispheres are frequently involved in the St. Louis, Toledo and Japanese encephalitis but are spared in lethargic encephalitis. These observations are of considerable differential value.

Summary: The distribution of the inflammation in the St. Louis, Toledo and Japanese encephalitis is much more diffuse than that in lethargic encephalitis. We agree with McCordock, Collier and Gray [2] and Kaneko and Aoki [1] that the St. Louis and Japanese type of encephalitis is histologically not identical with lethargic encephalitis and that differentiation is possible in many cases.

Clinical Observations.—Epidemiologically and clinically the epidemics of encephalitis in Toledo, St. Louis and Japan were identical. In each instance the outbreak was of short duration, lasting between two and one-half and three months, and occurred in the late summer or early

4. Spatz, H., in von Bumke, O.: Handbuch des Geisteskrankheiten, Berlin, Julius Springer, 1928, vol. 2, pt. 7, p. 157.

fall (Leake, Musson and Chope.[5] According to Kaneko and Aoki [1] the Japanese epidemics began "when the heat begins to decline." The great epidemic in 1924 in Japan started in July, reached its peak in early September and terminated in October.

According to Dr. H. G. Pamment, epidemiologist of Toledo, the epidemic in Toledo began the first week of August 1934; the last case was reported in the second week of October (table 1). The distribution of cases and fatalities according to the ages of the patients is given in table 2. The death rate was 28 per cent; the duration of the epidemic was sixty-nine days.

TABLE 1.—*Distribution of Cases with Respect to Time*

Week of		Number of Cases
August	6 to 12	1
	13 to 19	1
	20 to 26	0
	27 to Sept. 1	4
September	2 to 8	17
	9 to 15	9
	16 to 22	7
	23 to 29	6
	30 to Oct. 6	4
October	7 to 13	1

TABLE 2.—*Distribution of Cases and Deaths with Respect to Ages of Patients*

Age, Years	Number of Cases	Deaths
1 to 10	2	0
11 to 20	3	0
21 to 30	9	0
31 to 40	10	0
41 to 50	7	3
51 to 60	9	3
61 to 70	8	7
71 to 80	2	1
1 to 80	50	14

According to all authors, there is a striking increase in incidence and fatality with age, which we confirm (table 2). While there were no fatalities in the age groups below 40 years, the death rate was 87 per cent in the age group between 60 and 70 years. Japanese authors reported numerous cases in children. Among the patients in Toledo there were two children under 10 years.

The death rate was high in the Japanese epidemics, reaching from 60 to 63 per cent, as compared with 20 per cent in St. Louis, 23 per cent in Kansas City, Kan., 28 per cent in Toledo, 30 per cent in St. Joseph, Mo., and 37 per cent in Paris, Ill.

5. Leake, J. P.; Musson, E. K., and Chope, H. D.: Epidemiology of Epidemic Encephalitis, St. Louis Type, J. A. M. A. **103**:728 (Sept 8) 1934.

Clinical Course.—The clinical course is frequently stormy and of short duration. According to Hempelmann:[6] "The St. Louis cases were characterized by a rather sudden onset, with headache, high fever, stiff neck, mental confusion, tremors and other neurologic symptoms, but only occasionally transient ocular manifestations. Following a stormy course, in most instances rapid improvement occurred, leading to apparently complete recovery within two or three weeks and leaving no residual effects."

Kaneko and Aoki[1] and Beckmann[7] reported vague prodromal symptoms: headache, dizziness, insomnia or, in rare instances, drowsiness, nausea and vomiting, lasting a few days. Prodromal symptoms were present in both the cases reported here: The first patient complained of dizziness and headache, and the second patient, of severe headache.

Hempelmann[6] distinguished three clinical types of encephalitis: (1) the purely encephalitic or meningeal variety, (2) encephalitic symptoms following general infection and (3) the very mild (abortive) type. On the whole, this division corresponds with that of Kaneko and Aoki,[1] who distinguished between the severe and the mild type. The severe type "corresponds to the encephalomeningeal" group of Hempelmann,[6] in which "the onset is usually abrupt, with high fever, severe headache, rigidity of the neck, nausea and occasional vomiting and usually somnolence, mental confusion, tremors and difficulty in speaking." Kaneko and Aoki[1] described an identical picture: high fever, coma, a Kernig sign, rigidity of the neck and muscular twitching. All these symptoms were present in both cases reported here; both patients became comatose early in the course of the disease, and marked cervical rigidity and spasticity of the upper extremities were observed in the second patient. According to Kaneko and Aoki,[1] the rigidity may involve the entire body, but in most cases it is more pronounced in the upper extremities. In a fatal case, the body becomes flaccid toward the end. This was observed in case 2, in which the upper extremities became flaccid twenty-four hours before death.

The reflexes show few points of interest. According to Hempelmann,[6] the abdominal reflexes are frequently absent in the early stages, the Kernig sign is usually present and other reflexes may be exaggerated or diminished. This corresponds with the findings of Kaneko and Aoki.[1] In both cases reported here the reflexes were exaggerated.

Ocular symptoms are rare, according to all authors. Hempelmann[6] stated: "The pupils were usually small and equal, and they reacted well to accommodation although there was an occasional sluggish

6. Hempelmann, C.: The Symptoms and Diagnosis of Encephalitis (1932 St. Louis Epidemic), J. A. M. A. **103**:733 (Sept. 8) 1934.

7. Beckmann, J. W.: Neurologic Aspects of the Epidemic of Encephalitis in St. Louis, Arch. Neurol. & Psychiat. **33**:732 (April) 1935.

response to light." During the great Japanese epidemic of 1924, ocular symptoms were observed by Kaneko and Aoki [1] in only two cases. In the second case reported here the pupils were round, regular and equal and reacted to light.

Hempelmann [6] noted "moderately coarse or fine tremors, involving chiefly the hands, tongue and lips and persisting well into the second or even the third week." Kaneko and Aoki [1] reported clonic or tonic twitchings or tremors, usually involving the face and the extremities. This was pronounced in the second case reported in this paper, in which there were muscular twitchings of the face and body.

Retention or incontinence of the urine and feces occurs frequently (Hempelmann; [6] Kaneko and Aoki [1]). These symptoms were noted in the second case.

Mental confusion terminating in coma was frequently observed in St. Louis and in Japan. Both of our patients were comatose during almost the entire duration of the disease.

Hempelmann [6] stated: "The fever was highest in the first two or three days of the infection and then in most instances fell by rapid lysis, so that the normal was reached within a week or ten days of the onset." In some cases the fever was of irregular pattern and lasted from four to six weeks. The Japanese authors gave a similar description and distinguished three types of fever: (1) high continuous fever in fatal cases, (2) high fever in the first days with rapid lysis and (3) protracted fever, lasting several weeks.

Some of the Japanese authors observed cases in which there was no fever, which Kaneko and Aoki [1] did not accept as instances of this condition. However, in our case 1 the temperature fell to normal two days prior to death; so at least a partly afebrile course may occur in some instances.

The heart rate is usually moderately increased, but other deviations have not been reported.

Laboratory Findings.—The spinal fluid is usually clear, although slight cloudiness was reported by Japanese authors in some cases. The pressure is moderately increased; the cell count varies between 50 and 250, but occasionally much higher counts (from 400 to 1,100) have been reported. The globulin content is increased. The reaction to the colloidal gold test shows a moderate nonspecific curve. Examination of the blood usually reveals moderate leukocytosis (from 12,000 to 20,000 white cells); occasionally leukopenia has been reported (Kaneko and Aoki [1]).

Etiology.—Some Japanese authors expressed the opinion that the disease is caused by a filtrable virus which has been successfully trans-

mitted to apes, rabbits and guinea-pigs. According to Tsuda,[8] rabbits are most susceptible. Intracerebral inoculation produces fever and loss of appetite and weight and results in death.

Pathologically, the experimental encephalitis was characterized by hyperemia and edema of the meninges and the cortex. Histologic examination disclosed perivascular infiltration, degeneration of the parenchyma and neuronophagia. We agree with Kaneko and Aoki [1] that these changes were not due to encephalitis and had no diagnostic value, since they can be produced by the injection of foreign protein. The transmission of the Japanese type of encephalitis to animals has not been successful. From the pathologico-anatomic point of view, successful transmission must be followed by histopathologic changes identical with those noted in man. This takes place in experiments with poliomyelitis in monkeys and in experiments with rabies in different animal families.

The experiments by Webster and Fite [9] and others, who thought that they obtained successful transmission of the St. Louis type of encephalitis to the mouse, are not convincing. The histologic observations, as reported by these authors, were: (1) accumulations of mononuclear cells in the pia, around the blood vessels of the brain and spinal cord and in scattered foci; (2) damage and degeneration of the pyramidal cells of the cornu ammonis, the lobus pyriformis, the basal ganglia and the anterior horns of the spinal cord. In the latter region some of the neurons were covered with mononuclear cells. In our opinion these changes are not distinctive of encephalitis and can be noted frequently in normal animals.

At present the classification of acute encephalitis is confusing, since the term epidemic encephalitis has been applied to several different forms of the disease. It seems justifiable to readopt the old name, lethargic encephalitis, for the disease described by Economo and to designate the type observed in St. Louis, Toledo and Japan as encephalitis B, as proposed by Kaneko and Aoki.[1]

8. Tsuda, quoted by Kaneko and Aoki.[1]
9. Webster, L., and Fite, G.: Science **78**:463, 1933.

SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD IN PERNICIOUS ANEMIA

RESULTS OF TREATMENT IN SEVENTY-FOUR CONSECUTIVE CASES WITH CERTAIN CLINICAL OBSERVATIONS

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The efficacy of liver and liver preparations in the treatment for the anemia of Addison's pernicious anemia is generally recognized. The success of this therapy in the relief and prevention of glossitis is well known. It is generally conceded that the gastro-intestinal manifestations, weakness and general symptoms are all relieved by adequate treatment. There are, however, great differences of opinion about the response of the neurologic manifestations to the specific therapy. In 1927 Minot and Murphy [1] described definite improvement in the neurologic symptoms in cases in which the condition was of short duration and arrest of the progress of the lesion in others. Similar findings were reported by Graham [2] in 1928. Ungley and Suzman [3] (1929) described great improvement in the neurologic manifestations in the majority of patients in a group with pernicious anemia associated with subacute combined degeneration of the spinal cord, the less favorable results and progression of the lesion in the group being due to failure to persist in liver therapy or to infection. In a group of eighteen patients with pernicious anemia associated with definite subacute combined degeneration observed at the Toronto General Hospital, Farquharson and Graham [4] (1930) found gratifying improvement in many, especially in

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1. Minot, G. R., and Murphy, W. P.: Diet Rich in Liver in the Treatment of Pernicious Anemia: Study of One Hundred and Five Cases, J. A. M. A. **89**:759 (Sept. 3) 1927.

2. Graham, D.: The Treatment of Pernicious Anaemia, Canad. M. A. J. **19**:150 (Aug.) 1928.

3. Ungley, C. C., and Suzman, M. M.: Subacute Combined Degeneration of the Cord: Symptomatology and Effects of Liver Therapy, Brain **52**:271 (Sept.) 1929.

4. Farquharson, R. F., and Graham, D.: Liver Therapy in the Treatment of Subacute Combined Degeneration of the Cord, Canad. M. A. J. **23**:237 (Aug.) 1930.

those in whom the condition was of short duration, and arrest of the progress of the lesion in all patients who took the prescribed therapy. Like Baker, Bordley and Longcope,[5] they emphasized the benefit to be derived by persisting in the administration of large amounts of potent liver preparations. Recently, Strauss, Solomon, Schneider and Patek[6] described complete arrest of the disease in twenty-six patients with outspoken degeneration of the spinal cord who were given adequate liver therapy parenterally. Furthermore, they found that disease of the spinal cord did not develop in any of eighty patients with pernicious anemia who were given similar therapy for an average period of three years. Arrest of the progress of neurologic lesions, often with improvement, has been reported by many other authors.[7]

On the other hand, a great many investigators[8] have reported unfavorable results in patients receiving liver or other specific prepa-

5. Baker, B. M.; Bordley, J., and Longcope, W. T.: Effect of Liver and Liver Extract upon Symptoms and Signs Referable to Nervous System in Pernicious Anaemia, Minnesota Med. **13**:815 (Nov.) 1930.

6. Strauss, M. B.; Solomon, P.; Schneider, A. J., and Patek, A. J.: Subacute Combined Degeneration of the Spinal Cord in Pernicious Anemia, J. A. M. A. **104**:1587 (May 4) 1935.

7. (*a*) Richardson, W.: Pernicious Anaemia: Results of Treatment with Liver or Its Derivatives in Sixty-Seven Cases, New England J. Med. **200**:540 (March 14) 1929. (*b*) Davidson, S.; McCrie, J. G., and Gulland, G. L.: Treatment of Pernicious Anaemia with Liver and Liver Extracts, Lancet **1**:847 (April 28) 1928. (*c*) Bubert, H. M.: Subacute Combined Sclerosis: Report of Case, Associated with Pernicious Anemia, Improved by Murphy-Minot Diet, J. A. M. A. **90**:903 (March 24) 1928. (*d*) Smith, L. H.: Mental and Neurologic Changes in Pernicious Anemia: Report of Case with Treatment by Minot-Murphy Diet, Arch. Neurol. & Psychiat. **22**:551 (Sept.) 1929. (*e*) Lottig, H.: Zur Frage Beeinflussung der Rückenmarks-Erkrankung bei Biermerscher Anämie durch Leberdiät, München. med. Wchnschr. **77**:858 (May 16) 1930. (*f*) Staffieri, D., and Giacosa, R.: Resulta dos obteniodos con la hepatoterapia en la anemia de Biermer y el sindrome neurológico concomitante, Semana méd. **2**:906 (Sept. 26) 1929. (*g*) Pinéas, H.: Funikuläre Myelose bei perniziöser Anämie, Deutsche med. Wchnschr. **56**: 476 (March 21) 1930. (*h*) Starr, P.: Prevention of Spinal Cord Degeneration in Pernicious Anemia, J. A. M. A. **96**:1219 (April 11) 1931. (*i*) Meulengracht, E.: Prevention and Therapy of Lesions of the Spinal Cord in Pernicious Anemia, Ugesk. f. læger **95**:819 (July 27) 1933.

8. (*a*) Cohen, A. E.: Subacute Combined Sclerosis Progressive During Remission of Pernicious Anemia: Report of Case, J. A. M. A. **90**:1787 (June 2) 1928. (*b*) Seyderhelm, R.: Zur Behandlung der Zystitis und Pyelitis chronica mit Subkutin (Ritsert), Deutsche med. Wchnschr. **55**: 1704 (Oct. 4) 1929. (*c*) Dereux, J.: Syndrome neuro-anémique (avec atrophie optique). Echec du traitement par la méthode de Whipple, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:577 (May 13) 1929. (*d*) Krause, F.: Ueber das Versagen der Lebertherapie bei den funikulären Erkrankungen der perniziösen Anämie, Klin. Wchnschr. **8**: 2177 (Nov. 19) 1929. (*e*) Curschmann, H.: Die Nervenstörungen der Biermer-

(Footnote continued on next page)

rations, i. e., the development of neurologic symptoms, failure of symptoms to be relieved and even progression of the neurologic manifestations while the patient was under liver therapy.

Such variation of opinion indicates that there must be differences either in the treatment administered or in the interpretation of the clinical results. Treatment may vary in the dosage and potency of specific preparations used, details of which, unfortunately, have often been omitted in published articles, and in the care taken to ensure that the patient has followed the prescribed directions faithfully. In recent years the parenteral administration of potent extracts has facilitated the use of larger doses of active material and relieved any doubt about the patient's cooperation, allowing repeated observations of subsequent progress. There is variation also in the amount of rest prescribed, a factor of great importance in our experience.

Some observers attribute improvement to the increase in strength and sense of well-being associated with relief of the anemia. This fails to explain the definite improvement in physical signs noted by many authors and the fact that maximal improvement frequently occurs months after the hemoglobin content has risen to normal. For this reason it is important that patients should be examined frequently and followed for a long period before final judgment is passed on the effect of therapy. The duration and extent of the lesion before the initiation of liver therapy and the effect of any complicating infections should also be considered in evaluating the results.

The purpose of this paper is to report the results of treatment in seventy-four persons with pernicious anemia associated with definite subacute combined degeneration of the spinal cord who were admitted consecutively to the public wards of the Toronto General Hospital between June 1926 and June 1933 and to discuss in some detail certain clinical observations. It will be shown that the progress of degenerative changes in the spinal cord has been arrested in all patients who took the treatment as directed and that great improvement in the symptoms and signs of subacute combined degeneration occurred in many, most notably in those in whom the neurologic manifestations were of short duration. The nature of the reparative processes and the effect of various therapeutic measures and complications will be discussed.

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SURVEY OF MATERIAL

MANAGEMENT OF PATIENTS

On admission to the hospital, the patients were kept at complete rest in bed, and potent liver preparations were administered as soon as the investigation was completed. From the first it was customary to prescribe larger amounts of liver or liver preparations for persons with pernicious anemia associated with severe neurologic disease than was usually used for those with anemia alone. Very early it was noted that the most striking improvement had occurred in patients who had received the largest amounts of liver. Accordingly, the dose was quickly increased, and most patients in the series were given daily the broth or extract derived from 1,000 Gm. of liver, sometimes receiving in addition from ¼ to ⅓ pound (113 to 142 Gm.) of whole liver. In recent years, intramuscular injection of potent liver extract has supplanted the earlier oral therapy, and the minimum dosage has been the extract[9] derived from 200 Gm. of liver per week.

The period of complete rest was gradually lengthened. Since 1930 all patients with moderate or severe subacute combined degeneration have been kept at rest in bed for an initial period of three months, after which time exercise was gradually increased.

Since it was found that great improvement occurred commonly between the third and the sixth month of therapy, the patients were kept in the hospital for long periods, usually from four to twelve months. During their stay in the hospital the ingestion of the prescribed amounts of liver preparations was ensured. Opportunity was thus afforded for observation of the results of well controlled treatment.

Every precaution was taken to prevent the development of bedsores and infection of the urinary tract in patients in whom the disease was far advanced. When these were present, they were treated vigorously, sometimes with excellent results. Complicating conditions received appropriate treatment.

Massage, passive movement and reeducational exercises were used when indicated. In many cases, however, these measures were purposely omitted in an attempt to determine their value.

From the beginning the patients in this series have been under our direct observation. We made the neurologic and hematologic examinations and directed the treatment. These examinations were repeated usually every few weeks during the first year of treatment and at longer intervals thereafter.

CLASSIFICATION OF SUBACUTE COMBINED DEGENERATION OF THE CORD

Between June 1926 and June 1933, one hundred and seventy-two patients with pernicious anemia were admitted to the public wards of the Toronto General Hospital. The patients were all carefully studied,

9. The preparation used was that prepared by the Connaught Laboratories of the University of Toronto. Each cubic centimeter of this preparation contains the extract derived from 10 Gm. of whole liver. In many cases a special extract of double this concentration was used. It has been found repeatedly that intramuscular administration of the extract derived from 50 to 100 Gm. each week will induce a good reticulocyte response, followed by satisfactory increase in the amount of hemoglobin and the number of red blood cells.

and all survivors have been under observation within the past two years, with the exception of eleven whose whereabouts are unknown. Definite subjective and objective evidence of disease of the spinal cord sufficient to justify a diagnosis of subacute combined degeneration was found in seventy-four patients. Those with paresthesias alone have not been included in this series. Likewise, in the absence of definite subjective disability apart from paresthesias, patients showing only slight objective evidence of involvement of the nervous system, such as impairment of vibration sense, have not been included.

For purposes of description, subacute combined degeneration has been classified as mild, moderate or severe, according to the neurologic signs present when the patient was admitted to the hospital.

In the patients with mild subacute combined degeneration there was clumsiness or weakness of the limbs, with two or more of the following signs persisting in the absence of severe anemia and associated debility: gross impairment of vibration sense, impairment in sense of position, absence or diminution of the tendon reflexes, disturbance in the control of the sphincters and impairment of superficial sensation with or without mild disease of the pyramidal tracts. The patients in this group were able to walk without support but had a definite neurologic disability.

In the patients with moderately severe subacute combined degeneration there was (1) severe involvement of the posterior columns with little or no evidence of disease of the pyramidal tracts, or (2) moderate involvement of the pyramidal tracts and the posterior columns which was not, however, severe enough to incapacitate the patient completely.

In patients with severe degeneration there were signs of advanced disease of the posterior columns and the pyramidal tracts, the patients either being bedridden or requiring much support to walk short distances.

The patients may be classified according to their response to treatment as follows: those showing marked improvement, which consisted of freedom from symptoms and definite improvement in the objective neurologic signs; those showing moderate improvement, which consisted of definite improvement in the neurologic symptoms, with little or no change in the principal physical signs, and those showing slight or no improvement.

RELATION OF SUBACUTE COMBINED DEGENERATION TO ANEMIA IN ADDISON'S PERNICIOUS ANEMIA

It is notable that in a certain group of cases neurologic manifestations appear and progress to an advanced state before there are symptoms due to anemia. In twenty-five cases of this series the earliest symptoms of pernicious anemia were referable to degeneration of the

spinal cord. In many of these, however, well marked anemia had appeared before the patient was admitted to the hospital. It must be emphasized that there was definite macrocytosis in all, whether the hemoglobin content had fallen materially or not.

In the remaining cases the earliest symptoms of pernicious anemia were referable to anemia. In a number of these, neurologic symptoms appeared early and progressed as the anemia became worse. In others, subacute combined degeneration appeared abruptly with anemia but subsequent to previous relapses characterized by severe anemia alone (case 1). In three cases subacute combined degeneration developed after some degree of anemia without neurologic symptoms had been present almost continuously for from eight to ten years (table 1).

TABLE 1.—*Duration of Symptoms Referable to Anemia Before the Appearance of Symptoms of Subacute Combined Degeneration of the Cord*

Duration of Symptoms	No. of Cases
6 months	7
1 year	11
2 years	12
3 years	5
4 years	3
5-7 years	8
8-10 years	3
Total	49

Among our patients with pernicious anemia, on the other hand, are those who have suffered anemia in repeated relapses without showing evidence of subacute combined degeneration at any time. Despite this fact, however, it would appear that no patient with pernicious anemia is free from the danger of the development of subacute combined degeneration if treatment is neglected.

There is great individual variation in the susceptibility of different tissues to the deficiency disease pernicious anemia. In some patients severe glossitis is the earliest manifestation; in others, it is never a prominent symptom. Similarly, symptoms of anemia or subacute combined degeneration may predominate. Almost without exception, however, there is hematologic evidence of pernicious anemia—notably macrocytosis—irrespective of the degree of anemia.

It is not possible to predict in which cases of pernicious anemia subacute combined degeneration is likely to develop under inadequate therapy. The early histories in the forty-nine cases of subacute combined degeneration in which the onset was characterized by symptoms due to anemia differed in no way from the histories in other cases of pernicious anemia in which subacute combined degeneration did not subsequently appear.

The variation in the hemoglobin level of patients with subacute combined degeneration on admission to the hospital is shown in table 2. In fifteen of the seventy-four patients, the hemoglobin content lay between 76 and 95 per cent.[10] This number includes six (the average hemoglobin content, 80 per cent) who had received no previous liver therapy, seven in whom the inadequate dosage of liver preparations had not been increased after development of symptoms of subacute combined degeneration and two in whose cases liver therapy had been begun a few weeks before admission. In the majority of patients with pernicious anemia associated with subacute combined degeneration, the percentage of hemoglobin was over 55, whereas in by far the greater number with pernicious anemia without subacute combined degeneration the percentage of hemoglobin was under 40 on admission to the hospital.

DEVELOPMENT AND PROGRESSION OF SUBACUTE COMBINED DEGENERATION UNDER INADEQUATE LIVER THERAPY

Twelve patients in the series had been in the hospital on previous occasions suffering from pernicious anemia without subacute combined

TABLE 2.—*Percentage of Hemoglobin on Admission to the Hospital*

Percentage	No. of Cases
26-35	17
36-45	13
46-55	5
56-65	9
66-75	15
76-95	15
Total	74

degeneration. After discharge all failed to take the prescribed amount of liver,[11] and after varying intervals subacute combined degeneration developed. At this time anemia was usually present. In eleven cases there was a characteristic macrocytosis. In one case, however, the hemoglobin content was 92 per cent and the red cells numbered 4,400,000 and the blood film was not characteristic for pernicious anemia. It is noteworthy that in this case great improvement occurred subsequently under adequate treatment.

10. According to the hemoglobin standard of Haden (The Normal Hemoglobin Standard, J. A. M. A. **79**:1496 [Oct. 28] 1922), 100 per cent is equal to 15.6 Gm. of hemoglobin per hundred cubic centimeters.

11. The amount prescribed in cases of pernicious anemia without subacute combined degeneration was usually the daily ingestion of from ⅓ to ½ pound (142 to 170 Gm.) of whole liver or broth or extract from 500 Gm. of liver, or intramuscular injection of extract from 50 to 100 Gm. per week. In no patient taking this amount did subacute combined degeneration of the spinal cord develop.

Of the remaining sixty-two patients, twenty-three had received liver therapy before admission to the hospital and fifteen had received treatment before the onset of the symptoms of subacute combined degeneration. In eight the neurologic manifestations had progressed under inadequate therapy. All of these showed definite hematologic evidence of pernicious anemia even when the hemoglobin content was not materially reduced, indicating that the dosage had been inadequate for normal blood formation.

Subsequent to discharge from the hospital, twenty-two patients failed to take the prescribed treatment for long periods. Seven of these died of pernicious anemia associated with subacute combined degeneration and its complications; seven became worse but improved again on resumption of the liver therapy, although they failed to regain all that they had lost in the relapse. In the remaining eight cases, there was no progression of subacute combined degeneration, although a temporary relapse with some anemia occurred. It is interesting that in one patient relapse of subacute combined degeneration was occurring when the blood picture was not diagnostic of pernicious anemia (hemoglobin content, 88 per cent; red blood cell count, 4,600,000; no macrocytosis). In this case marked improvement once more followed the resumption of adequate therapy.

It is important to note that in our experience subacute combined degeneration has not developed in patients with pernicious anemia who have taken the prescribed treatment and that in our series in no patient with pernicious anemia associated with subacute combined degeneration have the neurologic manifestations progressed under similar circumstances.

RESULTS OF TREATMENT

Under treatment as already outlined, forty-one patients improved markedly, and sixteen showed moderate improvement; in nine, the improvement was slight or the disease remained stationary, and eight died shortly after admission. The relation of the degree of improvement to the severity of the lesion is shown in table 3.

It is clear that great improvement occurred most frequently in the cases of mild degeneration but that marked improvement did occur in a number of cases with severe disease of the spinal cord.

This is further illustrated in table 4, in which it is shown that the most important factor in prognosis is the duration of the neurologic symptoms. The great majority of patients showing marked improvement had suffered symptoms of subacute combined degeneration for less than one year. With longer duration of the neurologic lesion results were less satisfactory. No definite improvement occurred in the cases in which the disease of the spinal cord had been present for more than four years. One can give a good prognosis when the symptoms

and signs are only of a few months' duration no matter how severe, but with increasing duration the prognosis becomes less assured.

In several cases, striking improvement in neurologic symptoms and signs was noted within a few weeks of admission to the hospital, whereas in others definite improvement began only after many months. Commonly, greatest improvement occurred between the third and the sixth month of treatment. In general, the longer the duration of neurologic symptoms the more slowly did improvement occur.

It is impossible to overemphasize the value of early and vigorous therapy. This is well illustrated in case 1.

TABLE 3.—*Relation of the Degree of Improvement Under Therapy to the Severity of the Lesion*

Severity of Lesion	Improvement Under Treatment			Died Shortly After Admission
	Marked	Moderate	Slight or Stationary	
Mild	18	5	2	0
Moderate	15	7	3	3
Severe	8	4	4	5
Total 74 cases	41	16	9	8

TABLE 4.—*Contrast Between Degree of Improvement and Duration of Symptoms of Subacute Combined Degeneration*

Duration	Degree of Improvement			
	Marked	Moderate	Slight or Stationary	Died
Up to 1 year	34	9	1	0
1-2 years	5	5	3	1
2-3 years	2	1	1	4
3-4 years	0	1	1	1
4-5 years	0	0	3	2
Total—74 cases	41	16	9	8

CASE 1.—A. D., aged 39, a farmer, gave a history of pernicious anemia with typical onset in 1928; recovery took place under liver therapy in Scotland. The first admission to the Toronto General Hospital was in 1931 during a relapse with severe anemia. Neurologic examination gave entirely negative results. The patient was discharged, feeling well. He was receiving broth from 1 pound (453 Gm.) of liver daily. In September 1932 he felt well and had been taking broth from ¾ pound (340 Gm.) of liver daily. The hemoglobin content was 98 per cent; there was a slight degree of macrocytosis and no evidence of involvement of the nervous system. From this time, in spite of advice, the patient took only broth from ½ pound (226 Gm.) of liver daily. Early in December he began to notice increasing paresthesias, with stiffness and unsteadiness of the legs. These symptoms progressed rapidly, and on Dec. 30, 1932, he was readmitted to the hospital suffering from severe subacute combined degeneration of the spinal cord. He was unable to walk unsupported. The hemoglobin content was 60 per cent, and the red cells numbered 2,600,000. A smear was characteristic of pernicious anemia in relapse.

Repeated neurologic examinations during the first week in January 1933 revealed the following: The patient was unable to walk without support, the gait being markedly spastic-ataxic. Romberg's sign was immediately positive. Profound weakness of the legs was present with marked spasticity and frequent flexor spasms. The knee and ankle jerks were markedly hyperactive. Inexhaustible clonus was obtained at the knees and ankles. Typical bilateral dorsiflexion occurred on stimulation of the plantar surface. The sense of position in the lower limbs was defective, with no appreciation of the direction of passive movements of the toes. Vibration was not appreciated at or below the anterior superior iliac spines. Superficial sensation was impaired in patchy areas over the lower limbs. There was hesitancy of micturition.

Treatment.—Rest in bed for three months was prescribed. Liver extract was given intramuscularly as follows: the extract from 280 Gm. of liver weekly for the first two weeks; the extract from 600 Gm. per week for two months, followed by the extract from 400 Gm. weekly for six months; subsequently, the extract from 200 Gm. per week.

Response.—Rapid improvement occurred in the general symptoms. There was a reticulocyte response of 12 per cent on the fifth day. The hemoglobin content rose to 93 per cent by the twentieth day, with great improvement in the sense of well-being. By the end of the third week (January 20) the spasticity was less marked, and the flexor spasms were infrequent. There was some improvement in the sense of position of the toes and in superficial sensation. The clonus at the ankles and knees was variable.

By the middle of February, the spasticity had almost disappeared. The power in the legs was improved, and coordination (heel to knee test) was almost normal. Superficial sensation was nearly normal. The sense of position of the toes was only slightly impaired. There was no clonus at the knees or ankles, and the plantar reflexes and vibration sense were the same as on admission.

Because of the improvement in objective signs, it was anticipated that when the patient got out of bed the gait would be much improved. Some reeducational exercises were given in the last two weeks of March. On getting up during the first week of April, the patient walked well without support and was restrained with difficulty from doing too much. Further examination at this time showed: absence of paresthesias and of symptoms referable to the bladder, some return of vibration sense (table 5), good power at all the joints, good coordination, good sense of position and normal superficial sensation in the legs and feet. In response to the Romberg test, the patient swayed but did not fall. The knee and ankle jerks were less hyperactive, and the plantar reflexes were definitely modified, i. e., on the right there was some fanning of the toes but the general tendency was to plantar flexion and on the left there were dorsiflexion and fanning of smaller toes, the big toe being stationary.

In September 1933 the patient was free from symptoms except that he still tired rather more easily than in former years. The only remaining signs were the modified plantar responses and slight reduction in vibration sense of the legs and feet.

At the time of writing (June 1935) the vibration sense is practically normal, but the plantar responses remain as in September 1933; namely, on the right there is plantar flexion of all the toes with fanning, and on the left the big toe is stationary and there is slight dorsiflexion of the smaller toes with a tendency to fan. The patient is entirely free from symptoms and states that he feels and walks as well as he ever did.

It is interesting that in this case treatment was commenced within one month after the onset of symptoms of subacute combined degeneration. Improvement in the neurologic symptoms and signs began while the hemoglobin content was increasing and continued for months after recovery from the anemia. In this case the duration of symptoms was the shortest, the amount of liver extract administered the greatest and recovery the most complete of any in the series.

Even when symptoms are of long duration, marked improvement may occur if adequate liver therapy is continued. In the following case great improvement in the neurologic signs and symptoms began after eight months of treatment and continued for over two years.

TABLE 5.—*Summary Showing Frequency of Occurrence and Response to Treatment of Principal Signs and Symptoms in Sixty-Six Cases of Subacute Combined Degeneration*

Manifestations	No. of Patients Affected	Improvement			Became Worse
		Marked	Moderate	Slight or Stationary	
Paresthesia	66	44	15	7	0
Impairment of vibration	66				
Upper limbs	6	2	2	2	0
Lower limbs	66	5	12	49	0
Impairment of joint sense	61				
Upper limbs	24	11	10	3	0
Lower limbs	60	30	21	9	0
Disturbance of gait	59				
Ataxic	36	27	6	3	0
Spastic ataxic	18	13	3	2	0
Spastic	5	2	3	0	1*
Impairment of superficial sensation	44	35	5	4	0
Extensor plantar response	38	2	2	34	0
Disturbances of control of sphincter muscle	36	26	5	5	0
Psychic disturbances	33	19	6	4	4
Absence or diminution of ankle jerks	34	7	0	24	3
Absence or diminution of knee jerks	19	9	0	10	0
Exaggerated reflexes in legs	26	4	0	22	0
Clonus	8	6	0	2	0

* This patient (1926) received only one-fourth pound of cooked liver daily.

CASE 2.—Miss G. M., aged 52, a dressmaker, experienced symptoms of pernicious anemia in 1926. She took liver inadequately and failed to regain her former health. She began to have difficulty in walking in 1929, which gradually increased until she was admitted to the Toronto General Hospital in August 1931, when she had pernicious anemia in relapse (hemoglobin content, 35 per cent; red cells, 1,200,000) with severe subacute combined degeneration of the spinal cord.

She was dull mentally and was emotionally unstable. The gait was spastic-ataxic, and she was unable to walk without support. All limbs were weak, but there was no wasting. Joint sense was defective in the upper limbs and grossly impaired in the feet. Vibration sense was not appreciated at or below the anterior superior iliac spines. Superficial sensation was impaired below the

knees. The patient was unable to recognize the size or shape of objects placed in the hands. The ankle jerks were not elicited, and the knee jerks were elicited with difficulty. Typical dorsiflexion with fanning of the toes occurred on stimulation of the plantar surface. There was imperative micturition with frequency, hesitancy and occasional precipitancy.

Treatment.—Broth from 1 pound of liver and ⅓ pound of whole liver were administered daily until December 1934. Intramuscular therapy has been given since January 1935. The patient remained in bed for the first three months and then took graded exercises.

Response.—The blood picture improved rapidly, with the usual improvement in the sense of well-being. During eight months in the Toronto General Hospital, however, there was virtually no change in the neurologic symptoms and signs or in the mental and emotional state. At the end of this time (March 1932) the patient was transferred to the Toronto Hospital for Incurables as having a hopeless condition. Under continued therapy improvement occurred gradually. She became more stable emotionally, with improvement in memory, attention and perception. Power in all limbs increased, and the upper limbs regained normal joint sense. In the legs spasticity and ataxia became less marked, and superficial sensation returned to normal. The patient became able to walk well and was discharged from the hospital in the summer of 1933. She continued to improve until the summer of 1934, since which time there has been little change. At the time of writing (June 1935) the gait is virtually normal. The patient can walk 3 miles alone without discomfort. The Romberg sign is negative. Coordination and sense of position in all limbs are apparently normal. Vibration sense is faintly appreciated over both tibias. There is no disturbance in the control of the sphincters. The knee jerks and ankle jerks are all present, being more active on the right than on the left, and the plantar responses are still dorsiflexion.

This case of severe subacute combined degeneration is notable in that great improvement occurred when liver therapy in fairly large dosage was continued after the condition seemed hopeless. There was no complicating infection; no physical therapeutic measures or special reeducational exercises were used. The delayed improvement in the patient's condition, symptoms of which had been present for over two years, is in contrast with the immediate response in case 1, in which symptoms were of only four weeks' duration, although of equal severity.

In most cases the greatest improvement occurred between the third and the sixth month, but some improvement continued subsequently, gradually becoming less marked. Usually a stationary condition was reached in the second year of therapy, and this was maintained without relapse as long as the patient continued to take the prescribed treatment.

PRINCIPAL MANIFESTATIONS OF SUBACUTE COMBINED DEGENERATION AND THEIR RESPONSE TO TREATMENT

Improvement in patients with subacute combined degeneration obviously depends on the relief of many individual symptoms and signs. The frequency of occurrence of the principal manifestations and their

response to treatment are shown in table 5. It will be seen that with the exception of alteration of the reflexes and impairment of vibration sense, which returned toward normal in only a small proportion of cases, the other manifestations of the disease improved in most instances. The following discussion will be devoted to the consideration in some detail of individual symptoms and signs, with particular reference to their site of origin and the response to treatment.

CHANGES IN THE SENSORY SYSTEM

Paresthesias.—Numbness and tingling were most commonly encountered, but frequently sensations of freezing, burning, stinging and pricking were complained of in the limbs, either alone or associated with numbness and tingling. Well defined girdle sensations were not common, but paresthesias in the lower limbs often extended to a definite level on the trunk.

It is of interest to contrast certain features of the paresthesias in cases of anemia associated with subacute combined degeneration with those occurring in cases of pernicious anemia without other evidence of neurologic disease. In the ninety-eight cases of the latter, only six patients were free from paresthesias during the course of the illness. The remaining ninety-two had paresthesias of varying extent and intensity, but almost always the sensation was simply numbness or numbness and tingling confined to the extremities. In cases of anemia with subacute combined degeneration, however, the other types of paresthesia occur much more frequently and are usually more extensive. When the upper extremities are involved the patients often state that they have difficulty in feeling objects placed in the hands, a complaint rarely made in the absence of definite evidence of subacute combined degeneration. Paresthesias respond less rapidly to treatment in cases of anemia associated with subacute combined degeneration and tend to persist in the limbs otherwise affected by the disease. In general the longer paresthesias have been present before treatment, the more fixed they become. In the absence of subacute combined degeneration, however, paresthesias seldom persist long after recovery from anemia, except in a few cases in which there is well marked vascular disease.

Paresthesias have often been attributed to involvement of the peripheral nerves. Commonly they are confined to the distal parts of the limbs, but on careful inquiry one finds that the distribution is frequently segmental. Thus paresthesias may be confined to or be most intense in the great toes, the inner side of the legs, the outer side of the thighs or in one or two fingers. Even when the extremities are symmetrically involved in cases of long duration, the common manifestations of peripheral neuritis are lacking.

As previously mentioned, paresthesias in cases of anemia associated with subacute combined degeneration frequently extend to the trunk, and with recovery diminish first proximally and depart last from the distal parts of the limbs. This fact, together with the frequent segmental distribution of paresthesias and the observation that they are severe, bizarre and persistent in patients with objective evidence of disease of the spinal cord, would suggest involvement of the spinal cord as the basis for the production of the sensations. It is of some significance that paresthesias identical with those encountered in cases of pernicious anemia with or without subacute combined degeneration are frequently present in cases of disseminated sclerosis, and in the latter disease the origin is almost certainly in the central nervous system.

It has been shown by Orton and Bender [12] that degeneration of the sympathetic cells in the lateral horn of the gray matter of the spinal cord can be demonstrated commonly in cases of pernicious anemia with subacute combined degeneration. It is conceivable that paresthesias are in some way determined by a disturbance of the sympathetic nervous system. It is of interest in this regard that certain vascular phenomena sometimes occur in association with paresthesias. A number of patients with subacute combined degeneration of long standing who have suffered from paresthesia of the upper limbs of long duration show a pronounced reddening of the fingers and sometimes of the palms of the hands, suggesting a permanent change in the vasomotor tone of the part. Two of our patients with paresthesias in the upper limbs showed marked blanching of certain fingers on exposure to cold, which developed when they were suffering from pernicious anemia and recovered under adequate liver therapy. Several other patients complained of a modified form of the same disorder, although not to a degree which caused severe discomfort.

In certain patients who had previously been heavy cigaret smokers the resumption of smoking during recovery seems capable of aggravating paresthesias and causing a temporary recurrence of those which have subsided. The following case is recorded to illustrate this phenomenon and also because it serves as an example of the segmental distribution of paresthesias. The patient made an excellent recovery under treatment.

CASE 3.—Mr. C. F., aged 55, enjoyed good health until the summer of 1932, when he experienced numbness and tingling of both hands and numbness of the feet. A few months later his legs gradually became stiff and there was increas-

12. Orton, S. T., and Bender, L.: Lesions in the Lateral Horns of the Spinal Cord in Acrodynia, Pellagra and Pernicious Anaemia, Bull. Neurol. Inst. New York **1**:506 (Nov.) 1931.

ing difficulty in walking. Examination in March 1933 showed a thin man with icteric tint to the skin. The upper limbs were both weak, particularly the left. The sense of position was impaired in the left upper limb at all joints, being most marked in the fingers. The patient was unable to recognize the shape or size of objects placed in the left hand, yet texture was appreciated, and no gross impairment of superficial sensation was present. The legs were very weak and moderately spastic, with sense of position markedly impaired at all joints. Sensation to pinprick was absent on the inner side of the right leg from the ankle to a short distance above the knee. Pain on deep pressure was diminished in the right calf. Vibration was not appreciated at the anterior superior iliac spines or below. The tendon reflexes were all present, but the knee and ankle jerks were a little more active on the left side. Both plantar reflexes were dorsiflexion. The gait was spastic-ataxic, the patient requiring constant support to walk. The Romberg test was immediately positive.

Careful inquiry regarding paresthesias in this case showed that besides numbness and tingling of the hands, which were most severe in the left hand, and numbness and a swollen feeling in the feet, there were also areas of varying size of numbness and tingling on the thighs, hips and abdomen which were described as numb and freezing and a large oval area about the middle of the right shin anteriorly which felt numb. No objective sensory loss could be demonstrated in any of these areas. Around the waist was a feeling like tight constricting bands.

The hemoglobin content was 79 per cent; the red cells numbered 4,100,000, and smears showed macrocytosis characteristic of chronic pernicious anemia.

Treatment.—The patient remained in bed for two months and then took graded exercise. The liver therapy consisted of the ingestion of extract from 1,000 Gm. of liver daily till discharge from the hospital in June 1933; since that time he has received weekly intramuscular injection of extract from 200 Gm. of liver.

Response.—On this treatment there was progressive improvement. At the end of one month the paresthesias had almost disappeared from the feet, with the exception of the right big toe. They were still present in the other areas, but less marked. The patient was able to recognize pinprick on the right leg over the formerly dull area. Three months after admission to the hospital (June 1933) the paresthesias of the feet had disappeared; numbness was present in the fingers of the left hand and in the areas on the right shin, hips and thighs. The numbness and constricting sensations in the abdomen were still present. Gait was greatly improved, with no staggering on turning but only a slight widening of the base. By October 1933, the patient could walk 2 miles without fatigue and was improved in all respects. The paresthesias had completely disappeared, and there was no subjective stiffness in the legs. Improvement continued till September 1934, when examination showed no disability in the upper limbs. The gait was almost normal. The patient was able to stand on either foot unsupported. The sense of position was normal except for moderate impairment in the left great toe. Vibration was appreciated over both tibias but not at the ankles. The knee reflexes were equal, and the left ankle jerk was more active than the right. The right plantar response was dorsiflexion, and the left plantar response was of small range and consistently biphasic.

Prior to his illness the patient had been a heavy cigaret smoker. After discharge from the hospital he attempted to smoke occasionally, the last time in March 1934. After smoking part of a cigaret he felt

paresthesias of the extremities which were similar in site and character to those present in the active stage of the disease. These sensations lasted for several hours and gradually subsided. Although desiring to resume smoking, he has been prevented by the discomfort produced. The effect of inhalation of tobacco smoke in such cases may be accentuated by the fact that the resistance of habitual indulgence has been lost. However, it has been suggested [13] that tobacco smoke stimulates the sympathetic nervous system, variations in the susceptibility of persons being independent of the amount of tobacco habitually used. The response in this patient suggests that the site and character of the paresthesias (after smoking) may have been determined by previous degeneration of the sympathetic cells in the spinal cord.

Vibration Sense.—All patients were tested carefully for vibration sense at frequent intervals. A Symn fork has been used during the past five years, and the duration of appreciation of the sensation at the wrists, elbows, anterior superior iliac spines, vertebrae, tibias and ankles recorded in seconds. Vibration was found to be definitely impaired in the upper extremities in only six patients, all of whom were suffering from an advanced stage of subacute combined degeneration and showed other disabilities in the upper limbs as well. All the patients in the series showed gross impairment of vibration sense in the lower limbs, the majority having a complete loss of appreciation below the knees and a large number having no appreciation at the anterior superior iliac spines or sacrum as well. In few cases was the sensation appreciated even faintly at the ankles, and without exception the patients who showed gross impairment at the ankles and shins also had impairment at the anterior superior iliac spines, although it was usually less marked. In no case was postural sense more affected than the sense of vibration, although it was common to see patients in whom the sense of vibration was severely disturbed without much defect in postural sense. This contrasts with the observations on lesions affecting the spinal cord from without, e. g., extramedullary tumor of the spinal cord, in which severe disturbance of postural sense may be present with little impairment in vibration sense. For this reason impairment of vibration sense is a sign of diagnostic value as well as an early and consistent sign of subacute combined degeneration.

Of the ninety-seven patients with pernicious anemia without symptoms and signs sufficient to justify inclusion in the series with subacute combined degeneration, only nine showed marked reduction of vibratory appreciation in the lower limbs, although the great majority of the patients were over 45 years of age. A definite improvement in vibration

13. Barker, N. W.: Vasoconstrictor Effects of Tobacco Smoking, Proc. Staff Meet., Mayo Clin. **8**:284 (May 10) 1933.

sense occurred in four of these nine patients after treatment, indicating that the impairment was a manifestation of pernicious anemia. This suggests that gross impairment of vibration sense should be considered as a significant sign, particularly when the impairment progresses rapidly under observation.

It is important, however, not to attach too great significance to minor alterations in vibratory appreciation in elderly patients with pernicious anemia, for, as Pearson [14] has shown, the ability to perceive vibratory stimuli from the lower extremities becomes impaired in most persons after the fifth decade, the degree of impairment increasing with age. In controls in the same age group as our patients with pernicious anemia, not infrequently we have found some decrease in vibratory appreciation in the lower limbs in persons over 50 years of age. Unlike Pearson, however, we have seldom found the sensation grossly diminished or absent in these patients. Mild impairment of vibration sense in the lower limbs was frequently encountered in the ninety-seven patients with pernicious anemia without subacute combined degeneration. Although this was taken as an indication for careful observation of the patient, it was not considered to be indicative of involvement of the spinal cord requiring an increase in the amount of liver therapy.

Under treatment, a definite return of vibratory appreciation was observed in seventeen patients with subacute combined degeneration. The return was invariably gradual and occurred after improvement in other physical signs, notably postural sense. All of the cases in which vibration sense improved were cases in which the symptoms were of relatively short duration, although in four, manifestations of subacute combined degeneration were of more than one year's duration before treatment was instituted. The return of vibration sense was only partial in all instances, although 1 patient (case 1) with a history of symptoms of subacute combined degeneration of one month's duration almost completely recovered. This patient had been examined in January 1932, and vibration sense was found to be within normal limits of appreciation at the bony prominences. Throughout his illness vibration sense was never impaired in the upper limbs. The findings in the lower limbs at various times during the period under treatment are shown in table 6.

It will be noted that return of vibration sense was gradual compared with the rapid improvement in other symptoms and signs (see case report).

Sense of Position and Passive Movement.—Although commonly this function is impaired at all joints in the affected limbs, it is the rule to

14. Pearson, G. H. J.: Effect of Age on Vibratory Sensibility, Arch. Neurol. & Psychiat. **20**:482 (Sept.) 1928.

find maximal impairment in the distal joints. Accordingly, attention was devoted to the fingers and toes. A standard range of passive movement was used, and a record was made of the number of mistakes in judging the direction of twenty movements. When recognition of direction of movement was totally inaccurate, the ability to detect passive movement was graded according to the excursion required for its appreciation. The findings were rechecked at frequent intervals.

Striking improvement was observed in the upper and lower limbs in about 50 per cent of the patients affected. Most of those with history of subacute combined degeneration of relatively short duration showed complete recovery at all joints, but in those in whom the condition was of longer standing there was often recovery at the larger joints but some residual impairment at the periphery of the limbs. Even when

TABLE 6.—*Duration of Vibratory Appreciation at Various Bony Prominences in Case I (Symn's Fork)*

	Anterior Superior Iliac Spines		Midportion of Tibia		External Malleolus		Inner Malleolus	
	R.	L.	R.	L.	R.	L.	R.	L.
Date	Sec.	Sec.	Sec.	Sec.	Sec.	Sec.	Sec.	Sec.
20/ 1/32	21	22	19	18	19	21	20	20
Early December 1932			Onset of symptoms of subacute combined degeneration					
5/ 1/33	0	0	0	0	0	0	0	0
27/ 2/33	0	0	0	3	0	2	1	0
16/ 3/33	6	6	5	4	5	7	4	4
13/ 4/33	6	7	6	4	9	9	5	8
14/ 9/33	9	10	7	9	9	8	6	8
13/11/33	Not tested		10	9	9	15	12	9
18/12/33	Not tested		12	11	12	15	14	12
10/12/34	14	16	15	16	16	17	16	12
22/ 6/35	15	16	16	16	17	17	18	15

such objective evidence of disturbed joint sense was permanent, functional improvement often continued, indicating the importance of retraining.

Although improvement in joint sense is usually early, it may not reach its maximum for months or even years after the institution of treatment. The following case history illustrates this well.

CASE 4.—J. W., aged 36, a fireman, had recognized pernicious anemia in 1926; moderately severe subacute combined degeneration developed in 1929 under inadequate liver therapy. Three months after the onset, examination showed, in addition to well marked disease of the pyramidal tracts and loss of vibration sense in the legs, total inability to recognize the direction of passive movements of both great toes and less severe impairment of the sense of position at the ankles, knees and hips. While taking broth from 2 pounds (906 Gm.) of liver daily, he made a rapid recovery from the mild degree of anemia which was present and showed gradual improvement in the symptoms and signs of subacute combined degeneration. Six months after commencing treatment he was able to return to his difficult occupation, although on examination the sense of

position of the toes was still inaccurate for moderate movements. After two and a half years of liver therapy, sense of position in the left great toe was still grossly impaired, but he made only three mistakes in twenty passive movements of moderate range on the right side. At the end of four years of liver therapy, the movements of the right great toe were appreciated accurately, and only three mistakes were made in twenty movements on the left side. During the past two years this condition has remained stationary, but the patient is able to carry out his exacting duties.

The nine patients with defective joint sense who failed to improve satisfactorily without exception had severe subacute combined degeneration with long-standing symptoms. It may be significant also that five of these took the prescribed dose of liver for a few months only and subsequently took a smaller amount. Having seen improvement manifested late in other cases of severe involvement in which the patients persisted with the prescribed liver treatment, we think that possibly some of these five might have shown ultimate improvement in joint sense had they done likewise.

Stereo-Anesthesia.—This manifestation was present in nine cases, involving one hand only in six. In all but one case marked improvement occurred under treatment. Inaccurate recognition of the size and shape of objects placed in the hands was invariably associated with defective joint sense in the fingers. Recognition of texture was affected to some degree in all these patients, but except in two it was less affected than the ability to recognize size and shape. The two patients showed definite diminution of superficial sensation on the palms, in contrast to the other seven, whose disturbances of superficial sensation were of mild degree, usually consisting simply of impairment of two point discrimination, with possibly a qualitative impairment of sensation to light touch and pinprick as well.

Superficial Sensation.—A patient with subacute combined degeneration frequently shows impairment of superficial sensation, and it is surprising that this physical sign has received so little attention in the many descriptions of the disease. The degree to which it is impaired varies in different patients from a slight hypesthesia on the most distal portions of the extremities to an extensive loss of superficial sensation over a large part of the trunk and limbs.

In our experience it is uncommon to find superficial sensation impaired diffusely in a "glove and stocking" fashion on the limbs. But this, undoubtedly, does occur in certain cases and may be associated with increased tenderness on deep pressure over the extremities where sensation is reduced. These findings, when present, suggest that the peripheral nerves are involved by the process causing the disease of the spinal cord.

Much more frequently, however, the impairment of superficial sensation is not of a neuritic character but tends to have a distribution on the limbs and trunk which is sometimes segmental. In the absence of definite signs of disease of the peripheral nerves, sensory impairment of this nature may be assumed to have its origin in disease of the sensory tracts of the spinal cord. In this form of superficial sensory impairment the distribution usually conforms to three main types. It is probable that these three types differ only in degree, depending on the severity of the lesion, but for purposes of description they will be designated as A, B and C.

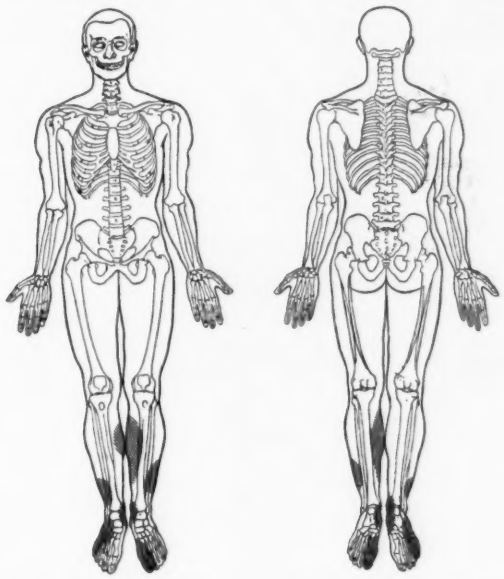

Fig. 1.—Diagram showing type A impairment of sensation. The patchy areas represent impairment of sensation to pin prick, heat and cold in a case of subacute combined degeneration. Light touch is very slightly affected.

All forms of superficial sensation may be impaired, but usually some dissociation is present with pain and temperature more affected than light touch.

Type A (twelve cases): This type of impairment of superficial sensation consists of small patchy areas of impairment of superficial sensation which were found most frequently on the lower limbs (fig. 1) but occurred also on the upper limbs and trunk.

Type B (fourteen cases): Apparently this type is a more advanced stage of type A. The region involved is more extensive, but careful examination shows a marked variation in the intensity of the sensory impairment in the affected areas. The result is areas in which sen-

sation is grossly diminished on limbs or trunk otherwise presenting a mild diffuse impairment (fig. 2). As in type A, these areas often show a segmental distribution.

Type C (six cases): This type of impairment of superficial sensation is unquestionably the result of a lesion of the spinal cord. It is found only in patients with severe subacute combined degeneration. Sensation is diminished on the lower limbs and terminates at a level on the trunk, usually about the middle portion of the abdomen. The level and degree of sensory impairment are frequently different on the two sides. Figure 3 shows the areas of impairment of sensation in a patient who subsequently died. A section from the spinal cord of this patient is shown in figure 4.

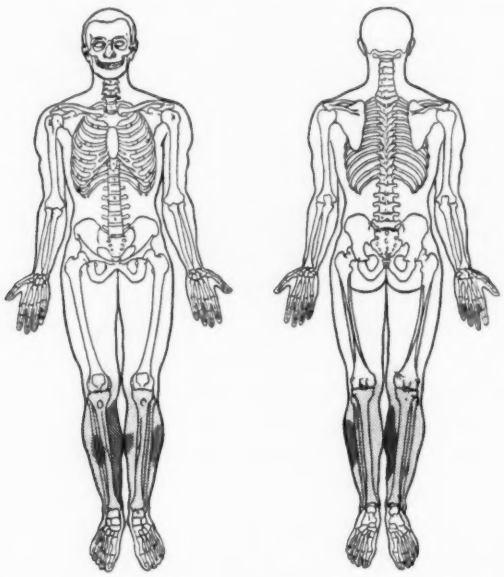

Fig. 2.—Diagram showing type B impairment of sensation. There is diffuse mild impairment of all forms of superficial sensation in the lower limbs in the lightly shaded areas. Pain and temperature sense are much more severely affected in the deeply shaded areas.

The relationship between the three types of impairment of superficial sensation is well shown by the findings in certain cases and is illustrated in figure 5. The patient had a diminution in sensation in the lower limbs extending to a level on the trunk and also various areas on the limbs and trunk where sensation was much more severely impaired. Under treatment, sensation was recovered in part, but at the time of writing, three years later, there is still a definite diminution

of sensation over most of the localized areas, although the diffuse impairment has completely disappeared.

The improvement in impairment of superficial sensation under treatment is usually rapid, and not infrequently complete recovery occurs. This is particularly true when the loss of sensation is confined to relatively small areas, as in type A. A patient with more extensive impairment of sensation may improve completely but commonly shows residual areas in which sensation is diminished. This is most likely to occur in a patient in whom the impairment extends up to a level on the trunk (type C).

In forty-four cases in our series definite gross impairment of superficial sensation was present. This does not include cases in which

Fig. 3.—Diagram showing type C impairment of sensation. There is extensive involvement of all forms of superficial sensation extending to a level on the trunk. The degree of impairment is much more marked on the right side than on the left.

only slight objective evidence of involvement was found, such as impairment of two point discrimination on the extremities or hypesthesia of the finger tips. Marked improvement was observed in thirty-five of the forty-four patients, the impairment of sensation either clearing up entirely or becoming insignificant. In the remaining nine patients in whom superficial sensation was disturbed, the impairment after adequate treatment was almost unchanged in four and still extensive, although improved in five. These nine patients all showed sensory impairment of the types designated as B and C.

CHANGES IN THE MOTOR SYSTEM

Power.—Apart from the generalized weakness associated with the anemia, impairment of strength of varying degree was found in the affected limbs in all cases of this series. A specific weakness in limbs showing other evidence of neurologic involvement is to be expected, and with one exception the power in the affected limbs improved under treatment. The exception was in a patient in whom contractures developed and who has been bedridden for six years. The improvement in power, which is such a prominent feature in the response to treatment, may be attributed to the improvement in general health as a result of

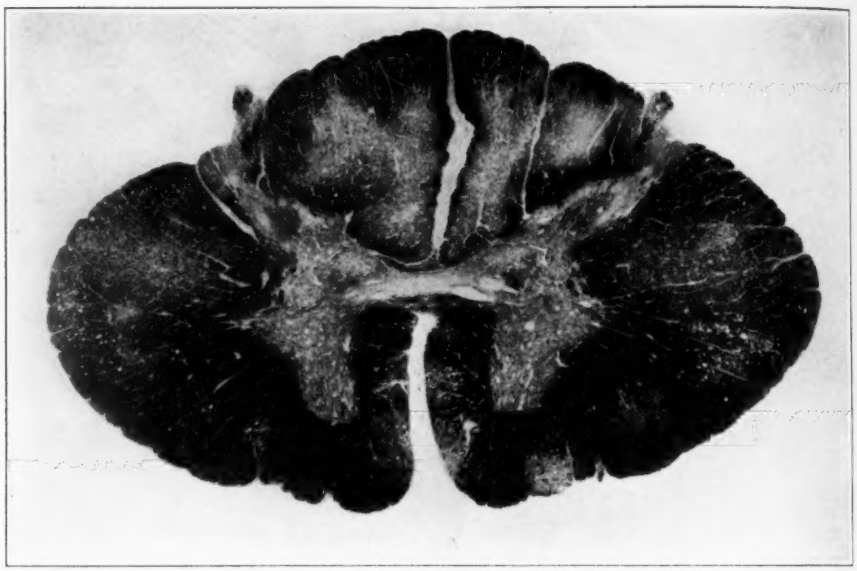

Fig. 4.—Section from the midthoracic segment of the spinal cord of a patient whose sensory impairment was as represented in figure 3. Note the gross involvement in regions of the ventral and lateral spinothalamic tracts on the left side. On the right side of the section less extensive demyelinization is evident in the region of the lateral spinothalamic tract. Weigert's stain; × 14.

recovery from the anemia or to actual improvement in the functional capacity of the nervous system. Whereas the former factor has some effect in all cases, it is our conviction that the latter accounts for the greater part of the return of strength. In certain cases in which the condition was of acute onset with signs of subacute combined degeneration confined to the lower limbs there may be a return of power in the affected limbs under treatment which closely parallels the recovery from anemia. But even in these cases the return in strength in the greatly weakened lower limbs is much greater in degree than in

the muscles elsewhere, whereas if recovery from the anemia was the only factor, one would expect an equal return of power in all muscles proportionate to their power before treatment was commenced. In cases in which the onset was slower one repeatedly sees the maximum improvement in power occur months after the blood picture has become normal.

Contractures.—Included in our series of patients are three who had severe flexion contractures of the lower limbs. All three were suffering from severe subacute combined degeneration when treatment was commenced, and the contractures developed while they were under treatment. One patient previously mentioned failed to respond to any

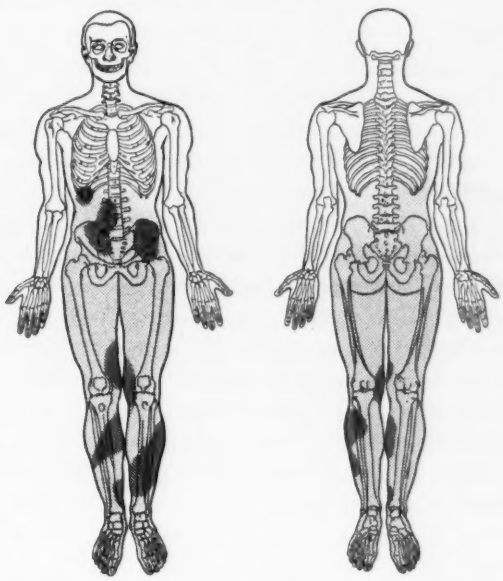

Fig. 5.—Diagram showing extensive mild impairment of all forms of superficial sensation extending up to epigastrium with areas (deeply shaded) on the abdomen and the lower limbs where pain and temperature are grossly impaired.

treatment, and the contractures are permanent and of extreme severity, but the two other patients were successfully treated. In both these patients the contractures developed and progressed rapidly despite physical therapy. When the contractures were approaching a right angle at the hip and knee, the legs were gradually straightened out at intervals with the patient under general anesthesia, and plaster casts were applied on each occasion. These were finally left in situ for several months in both instances. After correction, these patients have remained free from recurrence and have been able to walk for periods of four years and one and one-half years, respectively. In our experience this is the

most effective way of dealing with severe contractures, provided they are of short duration. Application of weights to the limbs is harmful, as it leads to increasing flexor spasms and aggravates the condition. Mild degrees of contracture present at the time the patient comes under observation will often subside under treatment with adequate amounts of liver and daily passive stretching by a physical therapeutist.

Gait.—Only six of the fifty-nine patients with objective disturbances of gait failed to show definite improvement while taking adequate treatment. In one of these patients, already mentioned, severe flexion contractures developed during hospitalization. In the remaining five patients the condition remained stationary or showed only a little improvement, but in three the duration of adequate treatment was short, and it was thought that further improvement might have occurred had treatment been maintained. The other two had severe disturbances of gait of long standing with extensive disease of the spinal cord.

Improvement in gait is dependent chiefly on improvement in power, tone and joint sense in the muscles of the lower limbs. There can be no doubt that improvement in general health as a result of treatment in a hospital and recovery from the anemia is a factor in improving the gait, but we feel convinced that it is only a partial explanation.

The question of reeducation must be considered in attempting to evaluate the results of treatment. We believe that this also is only a subsidiary factor and does not explain the marked improvement in many of our cases. Certain patients on admission to the hospital had little anemia but severe subacute combined degeneration. After three months in bed, during which time they received no reeducational exercises and were treated solely with liver, they were gradually allowed to be up. The improvement in gait after two or three days of attempting to walk was striking when compared with the condition on admission to the hospital. Examination of these patients during the period in bed had indicated that improvement in gait might be expected because physical signs, such as impaired joint sense and spasticity, had improved, and power in the limbs had returned. Rapid recovery such as this occurs only in persons in whom the subacute combined degeneration is of short duration and of relatively acute onset, but these patients show that improvement in gait can occur without reeducation being a factor at all. Usually, however, recovery is slow and gradual, and it is evident that the use of the limbs does assist in improving the gait. It should be remembered in this connection that no exercises are of value equal to the use of the limbs for their natural function in effecting improvement and that reeducational exercises should never be allowed to supersede encouragement to use the limbs by attempting to walk, which some patients who have been bedridden for a long time may be reluctant to do.

REFLEX CHANGES

Tendon Reflexes.—The tendon reflexes in the lower limbs were definitely diminished or absent in thirty-four patients. All these patients showed involvement of the ankle jerks, but in only nineteen were the knee jerks affected. After adequate treatment for a duration of six months or more, the knee jerks returned to approximately normal activity in six cases, and the ankle jerks, in seven cases. In none of these was the return of reflex activity associated with evidence of increasing involvement of the pyramidal tracts. In four other cases the knee jerks, which had previously been sluggish, became more active after several months of treatment. The increase in the reflex activity was accompanied by evidence of spasticity in one of these, and was interpreted as indicating developing disease of the pyramidal tracts. This occurred in the summer of 1926 while the patient was eating only a fourth of a pound of liver daily. In the other three patients the power and other functions of the lower limbs were improving at the time the reflex activity was increasing, and no evidence of spasticity was present.

When knee and ankle jerks returned, it was usual for the knee jerks to return first; occasionally, however, this order was reversed. The ankle jerks, which were previously markedly reduced, disappeared in three patients soon after treatment was commenced. The process interrupting the reflex arc was already well advanced in these patients; so the slight progression cannot be interpreted as failure of treatment when it is considered that all three improved markedly in other symptoms and signs of subacute combined degeneration, although the ankle jerks did not return. We have repeatedly observed that the presence or absence of tendon reflexes in the lower limbs is not necessarily an index of the severity of the lesion. Thus, in certain cases in which the legs are weak and flaccid and there is severe impairment of joint sense and vibration sense, the tendon jerks may be present; whereas in other cases, in which there are only a moderate amount of weakness, good joint sense and a reduction of vibration sense, the knee and ankle jerks may be absent.

Hyperactive reflexes in the lower limbs were noted in twenty cases before treatment was administered. In four of these the reflexes became less hyperactive under treatment. In the remaining twenty-two cases there was no definite reduction in the hyperactivity of the reflexes, although in most instances there was good clinical improvement in other neurologic manifestations.

Plantar Reflexes.—The response to plantar stimulation was dorsiflexion in thirty-eight cases. In testing the reflex, the outer side of the plantar surface of the foot was stimulated in all cases, and the responses were repeatedly checked and a description was recorded at intervals.

Two patients who had marked dorsiflexion and fanning of the toes before treatment was instituted showed a gradual return to the normal plantar flexion in both feet, in each case after several months of adequate treatment. The return of normal plantar responses was associated with improvement in the other manifestations of the disease.

Two other patients showed considerable modification of bilateral dorsiflexion responses after several months of treatment, but in both instances the responses became stationary, and at the present time, some years later, they show a preliminary dorsiflexion or fanning of the toes of a character which renders the reflexes still pathologic, although different from the well marked dorsiflexion which was originally present. Several other patients have shown lesser degrees of modification of dorsiflexion responses on one or both sides.

The patients most likely to show a modification of pathologic plantar reflexes are those in whom the symptoms are of relatively short duration before treatment is commenced. The improvement in these cases is usually marked in the first six months, and it is during this time that the dorsiflexion responses may show modification. In our experience the modification of the dorsiflexion response occurs early in the treatment if it is going to occur at all. A response which persists unchanged after a year or more is not likely to show any modification subsequently. In many cases in which the condition is of long standing there may be considerable return of power and lessening of objective and subjective spasticity under treatment, but usually no alteration in the original dorsiflexion responses can be demonstrated even if observation is continued over a number of years.

Abdominal Reflexes.—It was not possible to elicit the abdominal reflexes in a large proportion of our patients, but it was always difficult to be sure that this finding was of pathologic significance. It was extremely rare to find unilateral impairment of the abdominal reflexes. We frequently observed what has long been recognized in cases of subacute combined degeneration, i. e., that the abdominal reflexes may be bilaterally equal and active even when severe disease of the pyramidal tracts is evident in the lower limbs. In no cases were the abdominal reflexes observed to alter during treatment.

Sphincter Control.—The varieties of disturbances in micturition encountered included imperative micturition, hesitancy, precipitancy, retention and dribbling incontinence. Associated with these disturbances of micturition there was usually severe constipation but only occasionally incontinence of feces. In agreement with other observers [3] we found that these symptoms were greatly improved and frequently completely relieved in a high percentage of cases. The thirty patients with disturbances in the control of the sphincters who experienced definite

improvement made the following complaints prior to the commencement of treatment: precipitancy and imperative micturition, thirteen cases; dribbling incontinence of urine, six; incontinence of urine and feces, two; hesitancy and imperative micturition, five, and hesitancy and retention of urine, four.

The remaining six patients with disturbances in the control of the sphincters who failed to improve had subacute combined degeneration of long standing. Two of these patients neglected treatment after a few months. The outcome cannot properly be considered as a failure because a number of other patients obtained improvement in the control of the sphincters only after a long period of treatment.

The severe constipation so frequently associated with disturbances of micturition gradually improved in all these patients along with the improvement in control of the urinary sphincters.

We have observed frequently that a history of symptoms of long duration with evidence of severe subacute combined degeneration of the spinal cord does not preclude the possibility of relief from disturbances in the control of the sphincters if adequate treatment is administered. As an example of this the following case is cited. In this patient the signs of subacute combined degeneration were severe and of long standing, and the improvement in the control of the sphincters was the main response to treatment.

CASE 5.—Mr. A. S. commenced having symptoms of subacute combined degeneration in 1924 at the age of 40. He took small quantities of liver irregularly from 1926 until his admission to the hospital in 1929, but the symptoms progressed during this time. When he came to the hospital he was unable to walk and was found to have severe spastic paraplegia. The joint sense was grossly impaired in the lower limbs, and vibration was not appreciated at or below the ilium. He suffered from dribbling incontinence of micturition and severe constipation. The hemoglobin content was 81 per cent; the red cells numbered 2,800,000, and smears were characteristic of pernicious anemia.

Treatment.—One-half pound of cooked liver was administered daily, and the patient remained in bed for eight months. Then broth from 1 pound of liver and a varying amount of cooked liver were given daily.

Response.—During the three years following his admission to the hospital the patient showed gradual improvement and became able to walk with a stick, but the most striking improvement was in the control of the sphincters, which he regained over a period of years so that he became entirely free of complaints with regard to either the bladder or the bowel.

It should be emphasized that such remarkable recovery in the control of the sphincters is not unusual, and it is of particular interest that these distressing symptoms should improve so much, even when little demonstrable change in the signs of disease of the spinal cord in the lower limbs is evident.

PSYCHIC DISTURBANCES

Thirty-three patients in our series showed well marked disturbances in the emotional or intellectual spheres or both. The emotional upsets included anxiety states, varying degrees of depression and paranoidal trends. The intellectual defects consisted chiefly of impairment in memory, perception and attention. Nineteen of these patients improved definitely under treatment. Whereas the anemia may have been a factor in the production of the psychic symptoms in some instances, it was noteworthy that a proportion of the patients who improved had little anemia.

Several of the patients who improved only moderately, or not at all, had arrived at an age when senile changes were supervening. In two other cases of the group there was a history of emotional instability of long duration antedating the onset of pernicious anemia. In four cases the mental condition became worse while the patient was under treatment. In two of these, in which the history indicated a lifelong emotional instability, severe neuroses of the anxiety type developed. In the other two, severe psychoses apppeared (manic and paranoid, respectively), necessitating commitment to a hospital for patients with mental disease. These mental symptoms progressed while the physical condition of the patients was improving and appeared in no way different from similar mental disorders in patients without pernicious anemia.

RELATION BETWEEN IMPAIRMENT OF FUNCTION AND EXTENT OF PATHOLOGIC CHANGES IN THE CORD

In chronic degenerative diseases of the nervous system it is not uncommon to find pathologic changes quite out of proportion to the clinical symptoms and signs observed during life. Good function may persist during life in tracts subsequently showing marked pathologic change. Examples of this are seen in hereditary cerebellar ataxia and amyotrophic lateral sclerosis.

In cases of disseminated sclerosis it is not unusual to observe marked remissions in patients who have been totally disabled. In cases of acute anterior poliomyelitis recovery of function lost in the early acute stage of the disease is often observed. No one would claim that there has been regeneration of destroyed neurons in such cases, but that great improvement in function has occurred is beyond doubt. This is apparently the result of cessation of the active disease processes in the nervous system, and although pathologic evidence of severe destruction of nerve tissue may be found at autopsy the lesions are of quiescent type.

In cases of subacute combined degeneration great clinical improvement may occur even when the fiber tracts of the cord have been badly damaged. This is well illustrated in the following case:

CASE 6.—Mrs. A. F., aged 26, a housewife, was first admitted to the hospital in June 1927, with the complaint of general weakness, loss of weight, pallor,

numbness of the feet of three months' duration and periodic sore tongue and mouth for more than a year. Examination of the blood showed: hemoglobin content, 20 per cent; red cell count, 1,200,000; white cell count, 1,900, and a smear characteristic of pernicious anemia. The patient took a fourth of a pound of liver daily until October 1927, with marked improvement in her condition. From October 1927 to May 1928 she took no liver, and in February 1928 her symptoms commenced to recur. From May 1928 until September 1928 she took variable quantities of whole liver daily, and her general health improved considerably. From October 1928 to March 1929, she took some liver extract daily, missing only one week, in January. During November 1928 she experienced weakness of the legs and numbness of the feet which gradually increased in severity. By February 1929, her legs felt stiff and were so unsteady that walking was almost impossible. Her hands at this time were numb and clumsy, so that is was difficult to carry out movement with precision. She was admitted to the hospital in March 1929.

Examination in the hospital at this time showed a moderately well nourished woman whose perceptions were not dulled. Emotionally she was a little unstable. Power was defective in all limbs at all joints, but the impairment was much greater in the lower limbs. Coordination tests were poorly carried out in the lower limbs. The tone of the muscles of the legs was moderately increased, but it was not abnormal in the arms. The sense of position was grossly defective in the lower limbs. Vibration was not appreciated at the anterior superior iliac spines or below. Imperative micturition and frequent incontinence were present. The gait was spastic-ataxic. The Romberg test was immediately positive. The tendon jerks were present and equal. Both plantar reflexes were dorsiflexion. Examination of the blood showed: hemoglobin content, 65 per cent; red cell count, 4,500,000, and a smear characteristic of that for a treated patient with pernicious anemia.

Course.—The patient was given extract from 800 Gm. of liver daily, which she continued to take regularly until the time of death in December 1932. On this treatment there was continuous improvement. By October 1929, the paresthesias had greatly lessened. She experienced no difficulty in using her hands; imperative micturition had subsided, and there was occasional dribbling incontinence only on severe exertion or when coughing. Gait was much improved, although slight ataxia was still evident. In the Romberg test she swayed but did not fall. The right knee jerk was more active than the left. The plantar responses were still dorsiflexion. The sense of position was defective in the toes only, and vibration sense was absent in the lower limbs.

By November 1930, one and one-half years after commencing adequate treatment, the patient was doing all her own housework and taking long walks. Gait was not obviously impaired in ordinary walking, although staggering occurred if the eyes were closed. The sense of position was still impaired in the toes. Vibration was not appreciated in the legs. The right knee and ankle jerks were more active than those on the left. The left plantar response was definite dorsiflexion and the right plantar response showed less fanning and less marked dorsiflexion than one year previously.

Examination in October 1932, shortly before the operation which led to death, revealed that she was mentally alert and emotionally stable. There was no paresthesia. The upper limbs were normal in all respects. Power and coordination were good in the lower limbs and tone was slightly increased in the

muscles of the legs. The sense of position, although greatly improved, still was not accurate for moderate movements of the toes of the left foot but was good at all other joints. Vibration was faintly appreciated at the patellas, the anterior superior iliac spines and the sacrum. The right knee and ankle jerks were more active than those on the left. The plantar responses were as previously described. Gait was almost normal. The patient could walk ten paces with eyes shut without staggering. There was no disturbance in the control of the sphincters.

A gynecological operation was done on October 19. Septic complications developed after the operation, from which the patient died on Dec. 17, 1932. Liver treatment had been maintained up to the week preceding death. The fatal illness was in no way associated with pernicious anemia or subacute combined degeneration.

Autopsy.—Examination of the spinal cord showed it to be thin and atrophic, with anteroposterior flattening, particularly marked in the thoracic region (fig. 6). On section, severe degeneration of the myelin sheaths was seen in the white matter, affecting chiefly the posterior columns and the areas of the cord occupied by the crossed and direct pyramidal tracts. The degenerative process was most marked in the thoracic segments of the cord, with secondary ascending degeneration in the posterior columns of the cervical segments and descending degeneration of the pyramidal tracts down to the sacral region. Apart from ascending and descending degeneration, however, evidence of specific involvement in the form of patchy demyelinization of both lateral columns was seen in the highest cervical segments, and a similar finding was observed in the posterior columns of the sacral segments. There was no sign of an active process present in the degenerate areas. No vacuolation was seen (fig. 7), and stains for free fat revealed none present at any level. A dense fibrous reticulum was found in the degenerate portions of the cord, being most marked in the thoracic region (fig. 8). This was most striking in sections stained with Victoria blue. Longitudinal sections of the posterior columns showed fine fibrils running parallel with the nerve fibers, while in similar sections from the region of the lateral columns these fibrils assumed a criss-cross arrangement. The interstitial cells were relatively few in these areas as compared with the number of fibrils which had presumably arisen from them. The cells were mostly small astrocytes with such ill defined processes that it was not possible to trace the fibrils to their origin from individual cells. The whole appearance was suggestive of a replacement gliosis rather than a proliferative gliosis.

It is of interest that in this case the neurologic symptoms appeared and progressed rapidly while the patient was taking a liver extract in varying amounts sufficient to prevent development of severe anemia and associated symptoms. Although the neurologic manifestations had been present for only five months, response to treatment was delayed longer than in most similar patients in the series who received larger amounts of liver and had a longer period of rest in bed. The patient did, however, improve greatly over a period of three years.

Although there was definite improvement in signs, this was relatively small compared with the almost complete relief from symptoms. Definite signs of disease of the posterior and lateral columns persisted to the end.

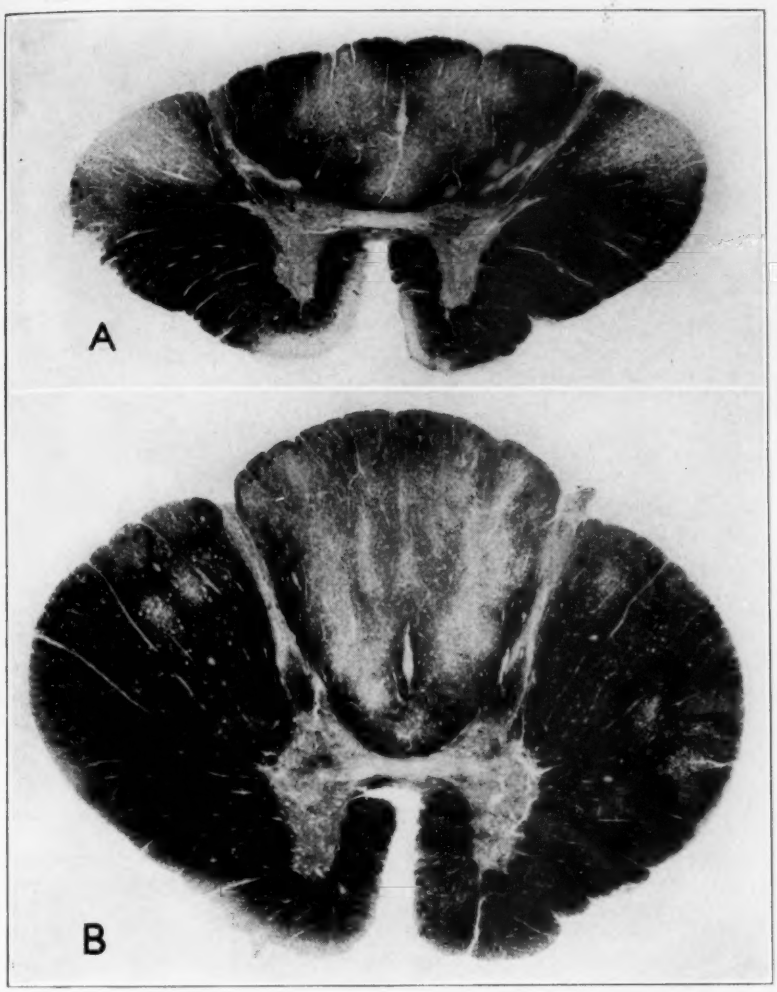

Fig. 6.—*A* shows a transverse section of a low thoracic segment of the spinal cord of Mrs. A. F., who was given liver therapy. There is severe demyelinization involving the posterior columns of white matter and the direct and crossed pyramidal tracts. The spinal cord is small and shows anteroposterior flattening. Weigert stain; × 14. *B* shows a transverse section of a low thoracic segment of the spinal cord of Mrs. M. M., who had severe subacute combined degeneration but received practically no liver treatment. The normal contour of the spinal cord contrasts markedly with that shown in *A*, which was cut from approximately the same anatomic level. Magnification, × 14.

Figures 6 *B*, 7 *B* and 8 *B* are reproduced from sections of the cord of a patient suffering from pernicious anemia associated with subacute combined degeneration of the spinal cord who died a few days after admission to the hospital. She had received no liver therapy prior to admission.

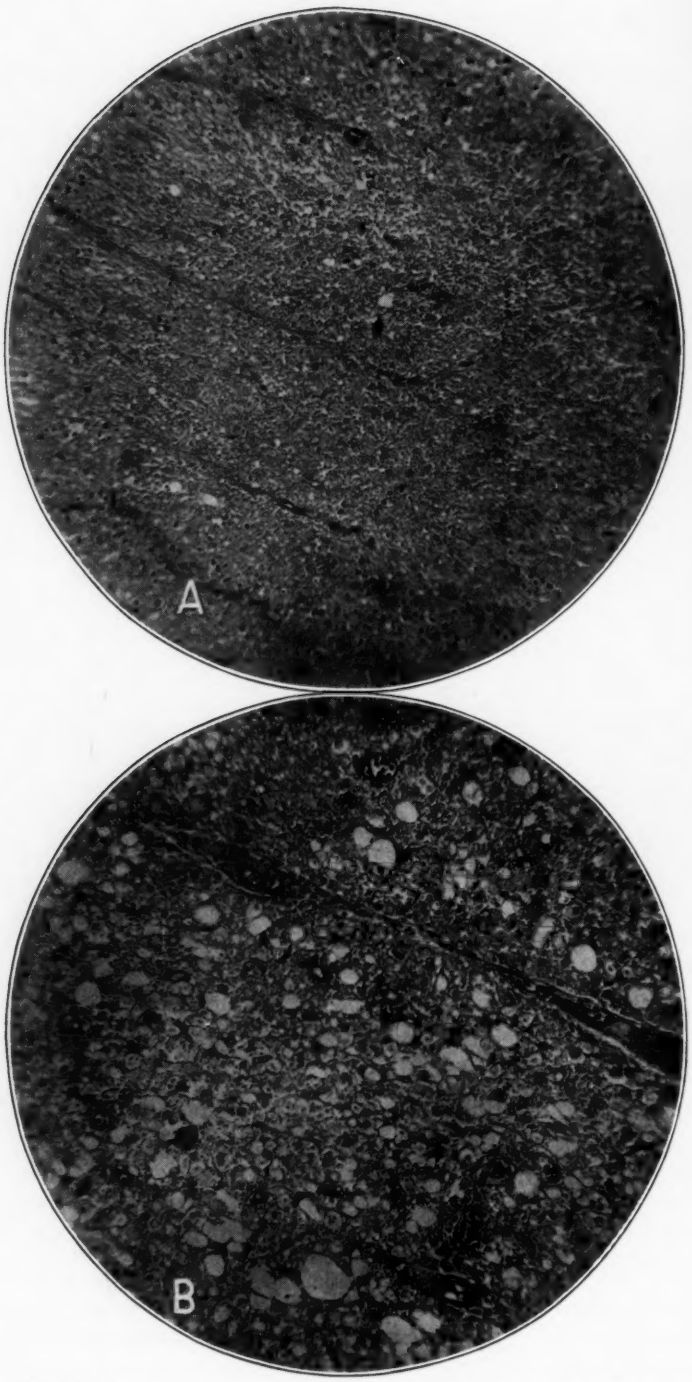

Fig. 7.—*A* shows a transverse section from a degenerate area of the posterior columns—same level as in figure 6 *A*. Note the condensation of tissue in the degenerated white matter with no evidence of activity of the disease. Hematoxylin and eosin stain; × 187. *B* shows a transverse section from a degenerate area of the posterior columns of the same thoracic segment shown in figure 6 *B*. Note the vacuolation indicating an active degenerative process. Compare with *A*. Hematoxylin and eosin stain; × 187.

It is instructive that there can be such good function when the fiber tracts are so badly damaged. It is important, however, to remember that the damaged portions of the cord showed no evidence of active disease but had the appearance of a healed lesion (figs. 7 and 8). It

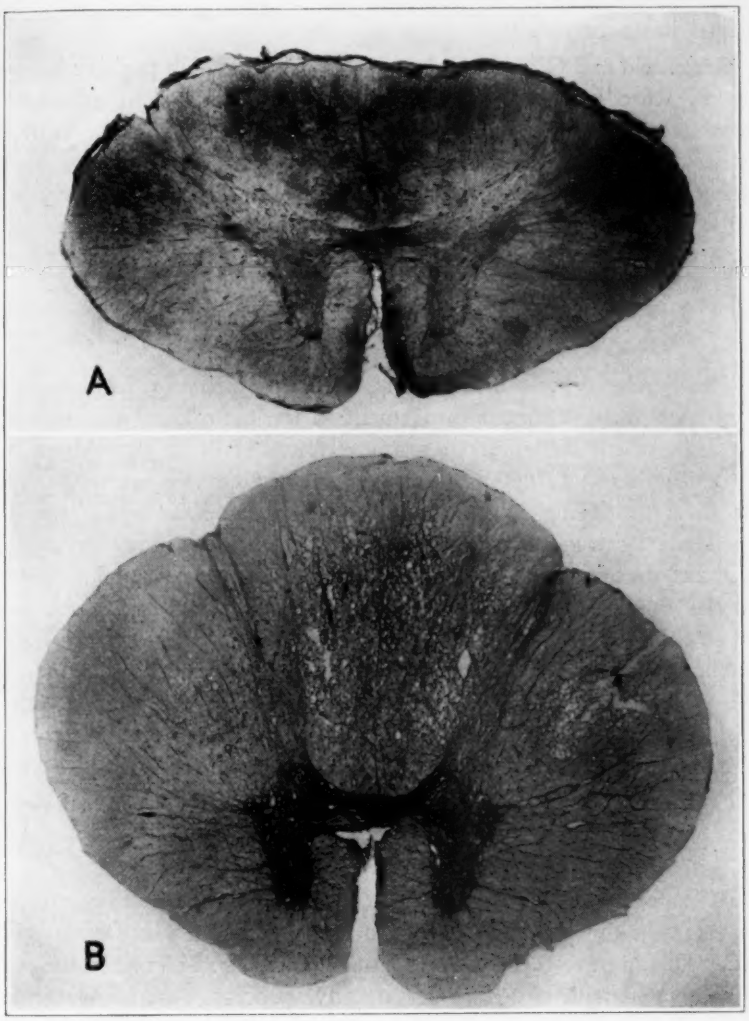

Fig. 8.—*A* shows a transverse section from same level as that in figure 6 *A*. There is marked gliosis in the regions where degeneration of white matter is present. Victoria blue stain; × 14. *B* shows a transverse section from same level as that in figure 6 *B*. Note the absence of gliosis. Compare with figure 8 *A*. Victoria blue stain; × 14.

is reasonable to assume that improvement in the function of the cord in this and in similar cases was due to the treatment that arrested the

process of degeneration and allowed healing to occur. Obviously much of the tracts had been completely destroyed, but the function of surviving fibers improved following the relief of swelling and edema of the active process. It is possible that in some fibers early degenerative change, sufficient to impair function, may be arrested before irreparable damage has occurred.

Greenfield and O'Flynn [15] described a case in which positive Babinski reflexes were present, although subsequent postmortem examination showed extremely slight lesions in the lateral columns, only one or two vacuoles being present in each section. They suggested that such a finding may explain the disappearance of this sign in an early stage of the disease. Apparently the change in function had been out of proportion to the visible structural change in the cord. Such a lesion might well respond to specific therapy.

GENERAL COMMENT

The results described show that in the majority of patients in the series there was definite improvement in the neurologic manifestations of the disease. Relief from symptoms was striking throughout, and frequently there was definite improvement in objective neurologic signs. The most gratifying improvement was in the ability to use the legs. This recovery in gait was dependent on improvement in power, postural sense and muscle tone of the affected limbs. Of almost equal importance was the improvement in the disturbance of the control of the sphincters that so commonly followed adequate treatment. Improvement in the less disabling sensory manifestations, both subjective and objective, was great. The most persistent abnormal signs were the altered reflexes which, however, did show improvement in some cases. It is notable that great improvement in motor and sensory function frequently occurred in the absence of any recovery of abnormal reflexes.

NATURE OF THE REPARATIVE PROCESS

Evidence has been submitted showing that great clinical improvement can occur in the presence of severe damage to the fiber tracts of the cord. This improvement is due primarily to the subsidence of the swelling associated with an active degenerative process, thus allowing undegenerated fibers to resume function. In this way it is possible to account for much of the rapid, early recovery in cases in which the duration is short. The gradual return of function in fibers that are mildly damaged but are capable of recovery probably contributes to both early and

15. Greenfield, J. G., and O'Flynn, E.: Subacute Combined Degeneration and Pernicious Anaemia, Lancet **2**:62 (July 8) 1933.

delayed improvement. In the majority of cases the greater proportion of fibers involved in the degenerative process are permanently destroyed. With optimal treatment, however, the surviving fibers can function with remarkable efficiency. This may be increased by retraining and by constant use of the limbs.

RECOVERY FROM PERIPHERAL NEURITIS NOT MAIN FACTOR IN IMPROVEMENT

Certain authors,[16] unwilling to believe that improvement in function of fiber tracts of the cord can occur, attribute the relief of neurologic symptoms of pernicious anemia to recovery from a lesion of the peripheral nerves. From observation of cases in which there is marked improvement we are unable to subscribe to this view, although fully appreciating the difficulty of distinguishing between symptoms referable to involvement of the peripheral nerves and those referable to the spinal cord in certain cases. The manifestations giving most difficulty in this regard are sensory disturbances and weakness. It has been shown that the paresthesia and superficial sensation often had a segmental distribution suggestive of an origin in the cord. When impairment of superficial sensation was present, it was frequently dissociated in character. Pain in the affected limbs and marked tenderness of the deep muscles, so common in cases of peripheral neuritis, were seldom present. It was not unusual to find the tendon reflexes retained in limbs showing well marked sensory involvement even in the absence of evidence of disease of the pyramidal tracts. When there was marked weakness of the limbs, even of many months' duration, wasting was never conspicuous. This would be very unusual were the weakness due to peripheral neuritis. Moreover, it is common to find recovery in power of the legs coincident with improvement in other physical signs of disease of the pyramidal tracts.

Improvement in the disturbances in the control of the sphincters and spasticity and changes toward normal in exaggerated reflexes, clonus and plantar responses indicate that definite improvement does occur in the function of the fiber tracts of the cord.

It is our belief that peripheral neuritis does not account for the principal neurologic manifestations of pernicious anemia and that relief

16. (*a*) Carmichael, E. A.: Discussion on the Treatment of Subacute Combined Degeneration, Proc. Roy. Soc. Med. **27**:775 (April) 1934. (*b*) McAlpine, D.: Review of Nervous and Mental Aspects of Pernicious Anæmia, Lancet **2**:643 (Sept. 28) 1929. (*c*) Grinker, R. R., and Kandel, E.: Pernicious Anemia: Results of Treatment of Neurologic Complications, Arch. Int. Med. **54**:851 (Dec.) 1934.

of the neurologic symptoms is due largely to improvement in the function of the fiber tracts of the cord.

IMPORTANCE OF IMPROVEMENT IN STRENGTH AND SENSE OF WELL-BEING

Relief from the symptoms of any disease is obviously facilitated by an increase in strength and a sense of well-being. Relief from anemia and from the general manifestations of pernicious anemia naturally allows the patient to make better use of the damaged nerve tissue. It is to be noted, however, that greatest improvement in cases of subacute combined degeneration occurred weeks and months after the rise in the hemoglobin content with disappearance of associated symptoms. In many cases there was definite improvement in the objective neurologic signs, indicating an actual change in the function of the fiber tracts. It is significant also that relapse of the neurologic symptoms need not accompany failure in health from other causes provided adequate liver therapy is maintained. Two patients with subacute combined degeneration who had improved greatly under treatment were subsequently readmitted to the hospital suffering from carcinoma of the stomach. They were given intramuscular liver therapy until the fatal termination. As they slowly failed in health and strength there was no progression of neurologic signs and symptoms.

REEDUCATION AND PHYSICAL THERAPY

Physical therapeutic measures, especially massage and passive movement, were used to increase the comfort of the patient, to improve the tone of the muscles and to protect the joints. They were helpful in relieving early contractures. Reeducational exercises seemed to hasten recovery, facilitating improvement in function of the damaged cord. That improvement was not due in any large degree to such measures alone is shown by the fact that some persons showing the greatest improvement had received neither physical therapy nor reeducational exercises. The most important reeducational measures, of course, arise from the patient's eagerness to make use of the limbs and to regain lost function.

REST

Before the introduction of liver therapy many physicians advised against a patient with subacute combined degeneration remaining in bed for long periods, fearing that he would become totally incapacitated. With liver therapy such fears become groundless, and rest assumes an importance in the treatment of pernicious anemia with subacute com-

bined degeneration just as in the treatment of other neurologic disease from which recovery may be anticipated. A patient should be kept in bed while the active degenerative process subsides under specific therapy and while the function of the surviving fibers slowly improves. Exercise should be increased gradually. While realizing the difficulty of assessing the actual value of rest in a patient receiving specific therapy, we believe that rest facilitates earlier recovery and may lead to greater ultimate improvement than would otherwise be obtained. Most patients kept in bed for three months walked better the first week they were allowed to be up than at the beginning of treatment, whether definite anemia had been present or not. In no case did the functional disability increase during the period of rest.

FACTORS THAT RETARD IMPROVEMENT

Complicating infections are known to exert a deleterious effect on many chronic diseases. It is common experience that recovery from anemia may be retarded by infection. The worst complications encountered in this series were infections of the urinary tract and bedsores, which sometimes led to a fatal termination. More frequently, however, improvement was delayed till the infection had subsided. Even after maximal improvement it would appear that the damaged spinal cord has less reserve and is more susceptible to toxic and other adverse influences. Temporary aggravation of latent symptoms has been observed during infection, following overexertion and on excessive use of alcohol and tobacco.

THE IMPORTANCE OF ADEQUATE LIVER THERAPY

It is impossible to overemphasize the fact that the administration of large amounts of liver preparations will prevent development and completely arrest the progress of subacute combined degeneration of the cord, as well as give rise to great improvement in many cases, particularly those in which the condition is of short duration. There is no reason to assume that the amount sufficient to control the anemia of pernicious anemia will be equally efficacious in the treatment of the neurologic manifestations. No one would consider relief from glossitis as a measure of adequacy for treatment of anemia. Similarly, one should not consider relief from anemia the measure of adequacy in treatment of subacute combined degeneration. Surely the optimal dosage is that required to prevent development, arrest progression and facilitate repair of all the lesions of pernicious anemia. Our experience would indicate that a larger amount may be required to promote healing of the neurologic lesion than is necessary for relief in average cases of

anemia. It is probable that patients with subacute combined degeneration vary in requirement as much as do those whose symptoms are referable to the anemia, but it is impossible to predict how much any patient may require. In patients with subacute combined degeneration there is no early indication of adequacy comparable to the reticulocyte response. It is safer, therefore, to administer large doses of liver to all patients, and this can now be done most effectively and with greatest certainty by intramuscular therapy.

SUMMARY AND CONCLUSIONS

The results of treatment in seventy-four consecutive cases of pernicious anemia associated with subacute combined degeneration of the cord have been described. Eight patients were virtually moribund on admission to the hospital and died within a few days. The remaining sixty-six patients were treated with large amounts of liver preparations and prolonged rest. During a period of from four to twelve months in the hospital and subsequent observation in a follow-up clinic, forty-one improved markedly and sixteen showed moderate improvement, while the condition remained stationary in nine. In no case was there real progression of the neurologic lesion. Improvement was maintained in all cases in which therapy was maintained as directed. These results fully confirm an earlier report.[4]

The most important factor in treatment is the administration of large amounts of liver preparation, the dose recommended being at least twice that required to bring about a prompt remission in a patient with anemia. Intramuscular therapy is the method of choice. The best results are obtained when the patient is kept at rest in bed during the early months of treatment.

The level of hemoglobin is not a satisfactory index of the adequacy of liver therapy. Subacute combined degeneration may develop and progress while a patient takes sufficient liver to prevent the development of definite anemia.

The changes that occur under treatment in the various symptoms and signs of subacute combined degeneration have been discussed. Evidence has been submitted indicating that relief of these manifestations is due to an improvement in function of the fiber tracts of the cord.

Attention has been directed to the manner in which superficial sensation is impaired. It is suggested that the tendency to segmental distribution of the impairment indicates an origin in the spinal cord.

Under adequate liver therapy a definite change in the pathologic picture occurs. All signs of active degeneration disappear, leaving an

apparently healed lesion. Associated with this change there is great symptomatic improvement in the majority of cases.

By administration of liver therapy in adequate amount, subacute combined degeneration can be prevented, its progression completely arrested and great improvement obtained, especially in cases of short duration. It is important that treatment be continued for prolonged periods before concluding that no improvement will occur.

Prof. Duncan Graham cooperated in this work. Prof. J. G. Fitzgerald, director of the Connaught Laboratories, University of Toronto, provided the liver extract used in this investigation.

ELECTRIC POTENTIALS OF THE BRAIN IN CERTAIN TYPES OF MENTAL DEFICIENCY

GEORGE KREEZER, PH.D.
VINELAND, N. J.

The present study was made to determine the properties of the electro-encephalogram associated with different types and levels of mental deficiency. This study was exploratory, its purpose being to determine the particular directions in which more detailed investigation would be desirable. The questions with which I was initially concerned are of two sorts: First, are there properties of the electro-encephalogram or of the cortical electrogram which characterize particular etiologic or clinical types of mental deficiency? Second, within any etiologic group what characteristics of the records, if any, vary with the intelligence level as measured in terms of Binet mental age? The types of mental deficiency which I shall consider here are the mongolian type and the so-called hereditary type. The selection of subjects as belonging to a group with a particular type of mental deficiency or level of intelligence is based on the examination of the psychologic and medical clinics of the Training School at Vineland. A subject was not classified as belonging in the group with the hereditary type of mental deficiency unless there was evidence of mental deficiency of hereditary origin in at least one other member of his family, with no evidence of another etiologic factor. This evidence is regarded as establishing a probability that the mental deficiency is of hereditary origin and is not regarded as conclusive.

A total of eighty-one subjects were examined in connection with this investigation. This group was made up of forty-one persons with the mongolian type of mental deficiency (twenty-one males and twenty females), eighteen males with the hereditary type of mental deficiency and twenty-two mentally normal subjects used as controls. Of the

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From the Department of Research, the Training School at Vineland, N. J. Mr. George B. Thorn, Superintendent of the Vineland State School, permitted us to include in our series a number of the patients in that institution.

Assistance in this study was furnished by a grant-in-aid from the National Research Council.

Read before the Section on Nervous and Mental Diseases at the Eighty-Seventh Annual Session of the American Medical Association, Kansas City, Mo., May 14, 1936, as part of a symposium on the electric potentials of the brain. The definition of relevant terms and a survey of the literature in this field were given in the introductory paper of the symposium.

normal subjects, fifteen were adults (ten males and five females), and seven were children ranging in age from 3 months to 9 years.

APPARATUS AND PROCEDURE

The apparatus used in the study consists of a vacuum tube amplifier and a Westinghouse oscillograph equipped for photographic recording. The standard sensitivity used in obtaining records was 10 microvolts per millimeter of deflection. Records are taken with the subject lying in a dark room with the eyes closed. A light strong enough to be seen through closed lids may be flashed on before him. A reference electrode is attached to the lobe of each ear and connected in parallel. The active electrode consists of a small coil of silver wire attached to a piece of rubber sponge and held on the head by means of an elastic headband. Contact with the skin is provided by means of a saline electrode paste. Electrodes of this sort are placed at three locations on the head about 1 inch (2.5 cm.) to the right of the median plane. The locations used are the region approximately over the right occipital area, that over the right motor area and that over the anterior part of the frontal area. The electrical activity over each of these regions is recorded in turn, a record of about forty seconds' duration being obtained with the lead over the occipital area and twenty seconds' duration with each of the other leads.

Analysis of the records is based on a preliminary labeling of successive intervals as belonging to one of three classes, to which I give the names regular sequences, irregular sequences and low level response. A regular sequence may be defined as a succession of 5 or more fundamental waves of about the same duration, as in a train of alpha waves. Low level response refers to portions of the record not exceeding the noise level of the amplifier. An irregular sequence refers to any other form of response. The total readable record consists of the total duration of the record minus the time occupied by occasional muscle potentials and visual stimulation.

On the basis of this preliminary analysis the following characteristics of the records are determined: (1) the percentage of time occupied by regular sequences, irregular sequences and low level response in the total readable record; (2) the ratio of the percentage of irregular sequences to regular sequences; (3) the frequency of waves in regular sequences (the frequency is calculated by counting only the fundamental waves and not the smaller waves of higher frequency often superimposed on them); (4) the average amplitude of waves in regular sequences in microvolts, measured from the trough to the peak; (5) the envelop types found enclosing regular sequences, in particular the percentage of time occupied by the spindle formation; (6) the effect of visual stimulation; (7) the presence of unusual types of waves, such as large waves of a frequency of less than 6 a second, found in certain of the records, particularly with the lead over the motor and the frontal region, and (8) the presence of beta rhythms, of a frequency of about 25 waves a second.

RESULTS

The results may be conveniently summarized as answers to the following three questions: First, do the principal types of rhythms found in the records of normal persons occur in the records of persons with the mongolian and those with the hereditary type of mental deficiency and at the various intelligence levels? In particular, do alpha

rhythms, of a frequency of about 10 waves a second, occur; do beta rhythms occur, and does the phenomenon of reduction or elimination of alpha waves with visual stimulation occur? The answer to all these questions is yes. These phenomena were found at all mental ages in the group of persons with the mongolian type of mental deficiency down to a mental age of 1.8 years. They were found in subjects with the hereditary type of mental deficiency down to a mental age of 4 years. The indications are, then, that in terms of a gross criterion such as the presence or absence of the principal rhythms the feebleminded persons of the types considered do not differ from the mentally normal.

The results of a more detailed analysis of the data in terms of the categories just mentioned may now be considered. Does the group of persons with the mongolian type of mental deficiency as a whole or the group of those with the hereditary type of mental deficiency as a whole show any distinctive differences from the mentally normal? No such distinctive characteristics were found.

Within each group of mentally deficient persons does any particular characteristic of the electro-encephalogram vary with the mental age in any region of the scale for mental age? The group of persons with the mongolian type of mental deficiency will be considered first. When all the subjects are arranged in order of mental age and the associated properties of the records examined, no indication of a variation with mental age is found down to a mental age of about 5 years. Below this level there are marked indications of differences of two kinds. First, the records show a much smaller percentage of regular alpha rhythms and a greater percentage of irregular sequences. Second, the records show the phenomenon of large waves of long duration, with a frequency of about 5 waves per second (fig. 4). This phenomenon is most marked in records obtained over the motor area and over the frontal area. It was not observed in the subjects with a mental age of more than 5 years. Figures 1, 2 and 3 illustrate the types of records obtained for mentally normal adults, persons with the mongolian type of mental deficiency of relatively high mental ages and persons with the mongolian type of mental deficiency of low mental ages, respectively, taken with the lead over the right occipital area.

The decreased abundance of regular sequences at mental ages below 5 may be illustrated by the following averages, for different groups of subjects, of the percentage of the total readable record occupied by regular sequences. For a group of ten mentally normal male adults an average of 52 per cent of the time was occupied by regular sequences. For the group of six persons with the mongolian type of mental deficiency of the highest mental age (between 6 and 7 years) the average was 48 per cent, but for the thirteen with a mental age between 4 and 5 years it was 21 per cent, and for the twelve with a mental age of less

than 4 years it was only 19 per cent. There is thus a pronounced decrease in the frequency with which regular sequences appear below a mental age of about 5 years.

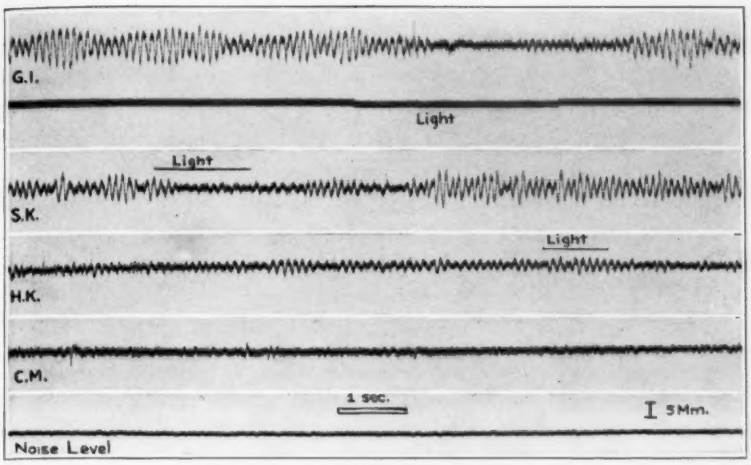

Fig. 1.—Electro-encephalograms of mentally normal adults, taken with the lead over the right occipital area.

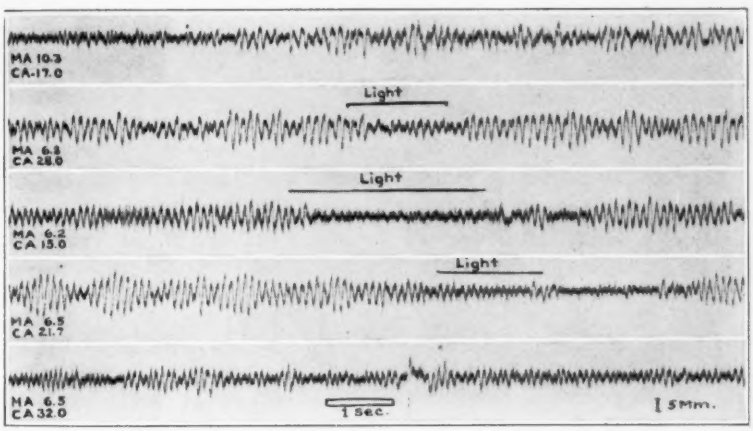

Fig. 2.—Electro-encephalograms of persons with the mongolian type of mental deficiency of a mental age of from 6.2 to 10.3 years, taken with the lead over the right occipital area. *MA* indicates mental age, and *CA*, chronological age.

The question may now be raised of the influence of chronological age on the percentage of time occupied by regular sequences. In order to determine the influence of chronological age within the group of

persons with the low grade mongolian type of mental deficiency, which is the group made up of subjects of a mental age of less than 4, the group was divided into two parts: a group of "young" persons, made up of five subjects between the chronological ages of 7 and 9, and a group of "old" persons, made up of seven subjects between the chronological ages of 18 and 45. The average percentages for these two groups are: 17 for the "young" group and 21 for the "old." There is a slight increase in the average percentage of regular sequences with the increase in the chronological age. The difference, however, is not statistically significant. The indications are, then, that the great difference in the average percentage of time occupied by regular sequences between per-

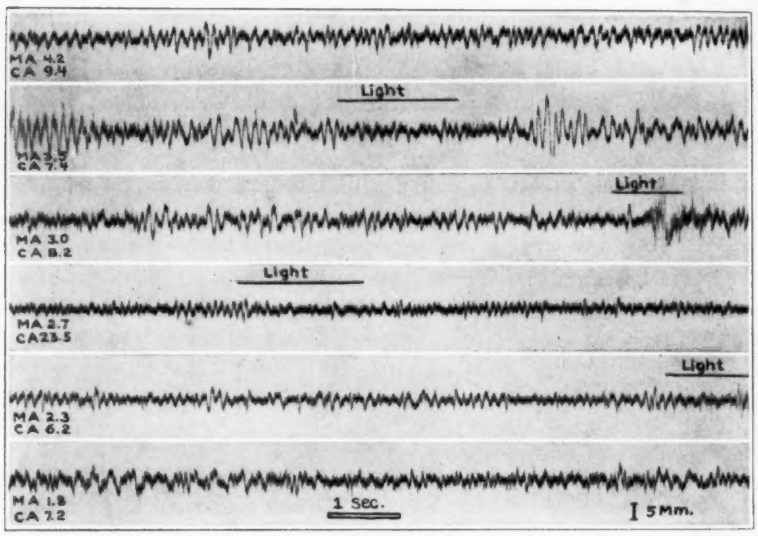

Fig. 3.—Electro-encephalograms of persons with the mongolian type of mental deficiency of a mental age of from 1.8 to 4.2 years, taken with the lead over the right occipital area. *MA* indicates mental age, and *CA*, chronological age.

sons with mongolism of lowest and those of highest mental age is a function of the difference in mental age.

As a further test of the influence of mental age, records were taken for a group of six mentally normal children, with chronological ages equivalent to those of the group of "young" persons with the mongolian type of mental deficiency. In contrast to an average percentage of 17 for the "young" persons with mongolism the mentally normal children on whom observations were made showed an average percentage of 54, indicating more than three times as great a prevalence of regular alpha rhythms. There was practically no overlapping between the two groups,

the highest percentage in the group of "young" persons with the mongolian type of mental deficiency being 31.5 and the lowest percentage in the group of mentally normal persons being 31. These data,

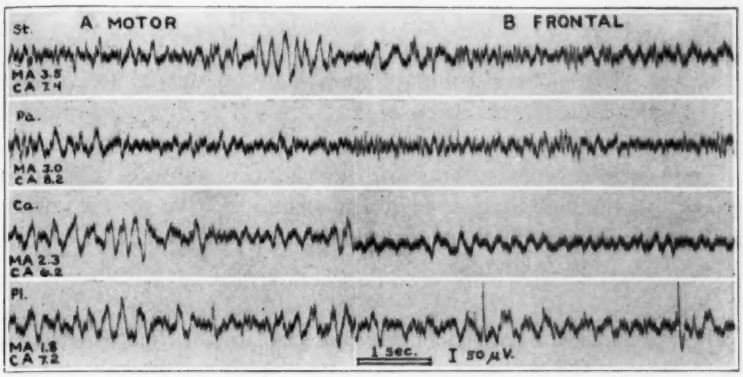

Fig. 4.—Records illustrating the low frequency waves obtained over the motor and the frontal area of certain of the persons with the mongolian type of mental deficiency. The waves are of long duration, with a frequency of 4 or 5 a second. *A*, records obtained with the lead over the motor area. *B*, records obtained with the lead over the frontal area. *MA* indicates mental age, and *CA*, chronological age.

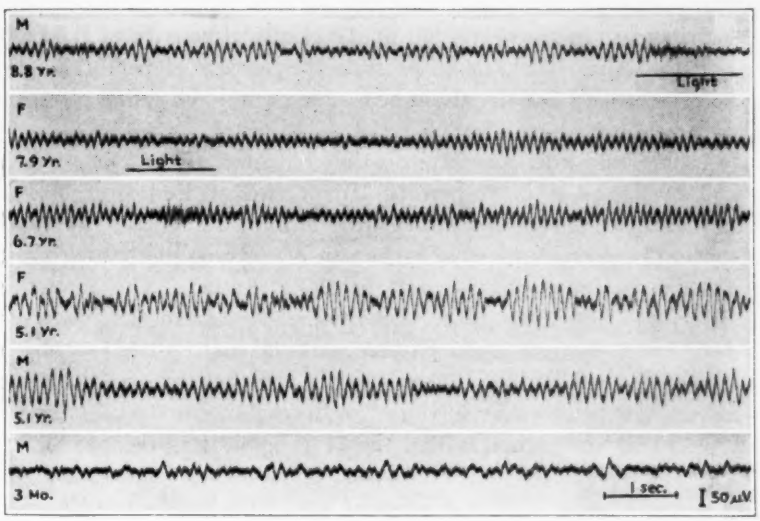

Fig. 5.—Electro-encephalograms of mentally normal children of a chronological age of from 3 months to 9 years, taken with the lead over the right occipital area. *M* indicates male, and *F*, female.

too, point to the influence of mental age on the wave pattern of the electro-encephalogram. Figure 5 illustrates the types of records obtained for mentally normal children.

With respect to the other properties of the electro-encephalogram examined—the average frequency and amplitude of the waves in regular sequences, the prevalence of the spindle type of envelop enclosing the waves and the influence of visual stimulation—no variation with mental age was observed. In the case of frequency, for example, I found a range for the total group of subjects of between 7.3 and 12.6 waves per second, with no consistent relation between mental age and frequency, independently of chronological age. The frequencies for the group of normal children were lower than those for the normal adults.

The electro-encephalograms of the eighteen subjects with mental deficiency of the hereditary type so far examined have shown few noteworthy features beyond those already mentioned.

COMMENT

These results are of particular interest in the light of Berger's report [1] that at about the age of 4 years the electro-encephalogram of the child first acquires the characteristics found in that of the normal adult. The implication of our results is that the decisive factor in this transition is the increase in chronological age only so far as it is accompanied by an increase in mental age. Expressed more accurately, it may be supposed that at about the age of 4 years changes in cortical structure and function appear which, on the one hand, condition a marked increase in the regularity of the electrical activity of the cortex and, on the other hand, make possible the successful performance of the tasks necessary for the attainment of a mental age rating of 4 years or more.

It is interesting to speculate on the character of the change in the cortical system that is responsible for this increased prevalence of regular sequences in the cortical electrogram. A satisfactory hypothesis will naturally depend on what is known concerning the nature of the physiologic system responsible for the alpha rhythm. The latter question itself still lies in the realm of hypothesis. Adrian and Matthews [2] have suggested that the alpha rhythm must depend on the synchronous activity of a considerable number of cells and that the abolition of the rhythm may depend on the change from synchronous to asynchronous activity among the cells. If this theory is applied to the present case it might be suggested that in persons of a mental age of less than about 4 years the factors predisposing to a synchronous or organized activity of a group of cortical cells are absent or deficient. The separate cells may be thought of as discharging more or less independently of

1. Berger, H. Ueber das Elektrenkephalogramm des Menschen, München. med. Wchnschr. **79**:1636 (Oct. 7) 1932.

2. Adrian, E. D., and Matthews, B. H. C.: The Berger Rhythm: Potential Changes from the Occipital Lobes in Man, Brain **57**:355, 1934.

each other and so leading to resultant cortical activity of the irregular or random type. But how is one to account then for the fact that regular sequences of alpha waves occur at all in persons of a mental age of less than 4 years, even though rarely? One might take recourse to a statistical theory and suppose that, as in certain physical systems in which a large number of units are operating independently, the independently beating units will, under the operation of so-called chance factors, occasionally beat in unison and accordingly produce a detectable alpha rhythm. In the subjects of the higher mental ages, on the other hand, one may suppose some organizing factor to be present that tends to keep the multitudes of cells in step a large portion of the time. In a relatively small number of mentally normal persons, however, still other factors tending to prevent regular sequences must be present, as is evidenced by the fact that a small percentage of mentally normal subjects fail to exhibit a predominance of regular sequences. Among such mentally normal subjects it is desirable, however, to distinguish between those who merely provide a low level response, the significance of which is as yet indeterminate, and those whose records are definitely irregular and of appreciable amplitude. I have the impression that the type of irregular record found for such mentally normal subjects is different from that for subjects of a mental age of less than 4. But further work is needed here in the direction of a more precise description and classification of the possibly different kinds of irregular sequence.

It is apparent from the discussion that the results obtained provide no basis as yet for a diagnosis of mental deficiency at any level by means of the electro-encephalogram. The differences found at the lower end of the mental age scale are essentially statistical. They must depend for conclusive demonstration on a sufficiently large sampling of subjects and the use of statistical indexes of reliability. The differences thus found between averages point to the existence of factors associated with certain variations in mental age and not to pathognomonic symptoms. The determination of the physiologic nature of these factors must rest with further physiologic inquiry. This survey has pointed to the regions in which more concentrated inquiry would be desirable. It is to be hoped that a focusing of investigation on these regions will enable the neurophysiologist to profit from his electrical tools in learning something of the physiologic basis of mental deficiency.

ACTION POTENTIALS OF THE BRAIN

IN NORMAL PERSONS AND IN NORMAL STATES OF CEREBRAL ACTIVITY

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AND
PAULINE A. DAVIS, M.A.
BOSTON

The human brain generates electrical potentials strong enough to be detected through the intact skull. A record of these potentials is analogous to the familiar electrocardiogram and, like the latter, furnishes a convenient external index of the activity of a hidden organ. The fact that the brain of a living animal is the seat of electrical activity was discovered by Caton [1] in 1875, but, although the observation was repeatedly confirmed and considerably elaborated by other workers, it was completely ignored by most neurophysiologists until the last decade. Then, with the aid of the new and powerful electron tube amplifiers developed by radio communication engineers, the field was reopened by Fischer [2] and his pupil Kornmüller in Germany, Adrian [3] in England and Bartley and Newman,[4] Bartley and Bishop [5] and others in this country. Particular credit from the medical point of view is due to Berger,[6] a neuropsychiatrist of Jena, Germany, who showed that characteristic electrical waves can be recorded from the intact human scalp. These electrical fluctuations are much weaker and also far more complex than those of the electrocardiogram, but they hold fascinating promise for the analysis of cerebral function and neurologic diagnosis.

The potentials from most human heads amount to only some fifty millionths of a volt. Fortunately, this is well within the range of modern amplifiers, and one can obtain records on photographic film or traced directly in ink on a moving ticker tape. In such records waves

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This study was furnished assistance by a grant from the Josiah Macy Jr. Foundation.

1. Caton, R.: Brit. M. J. **2**:278, 1875.
2. Fischer, M. H.: Arch. f. d. ges. Physiol. **230**:161-178, 1932.
3. Adrian, E. D.: Electrical Activity of the Nervous System, Arch. Neurol. & Psychiat. **32**:1125-1136 (Dec.) 1934.
4. Bartley, S. H., and Newman, E. B.: Science **71**:587, 1930.
5. Bartley, S. H., and Bishop, G. H.: Am. J. Physiol. **103**:159-172, 1933.
6. Berger, H.: Arch. f. Psychiat. **87**:527-570, 1929.

usually recur at certain regular frequencies. Most prominent is a rhythm of approximately 10 a second, nearly constant in frequency for any individual person. This is variously known as the "Berger rhythm," the "alpha waves" or the "10 cycle rhythm." Less prominent, because lower in voltage, is a faster rhythm, with a frequency of about 25 waves a second, called by Berger the "beta waves." Other less constant and less regular waves and rhythms appear, and one can speak of "mixed" or "random" activity.

Passing over for the moment the technical details of placement of electrodes, elimination of extraneous electrical disturbances, etc., consideration may be given to some characteristics of these cerebral waves and rhythms.

First is the ceaseless continuity of activity. Hour after hour, sleeping and waking, the electrical pulsations continue. Individual cells and units may pause and rest, for all one knows, or their pattern of activity may shift, but the normal cortex as a whole is never inactive electrically. Short of causing permanent damage, it is only by almost complete anemia of the brain or nearly lethal anesthesia that we have been able to abolish electrical activity in the cortex in experimental animals.

The details of the pattern of activity depend on which region one examines. Kornmüller [7] performed careful experiments on the exposed brains of rabbits. He found that a region which is homogeneous from the histologic point of view gives the same general pattern of electrical activity throughout but that when the exploring electrode passes over a boundary, e. g., at the edge of the area striata or of the motor cortex, the pattern of activity alters abruptly. The same tendency is more or less evident in the human head, for although the presence of the skull completely obscures sharp transitions,[8] the occipital region is usually the source and center of the smooth-rolling 10 a second waves,[9] while the 25 a second waves are best seen over the motor area and the frontal area also yields many sharp, quick waves.[10] On the other hand, the various regions are not completely independent, and the alpha waves from the area striata may spread far into the parietal and even to the frontal lobe. The violent electrical disturbances of strychnine poisoning in animals [11] and of epilepsy in human subjects spread from region to region like fire through hay-fields.

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7. Kornmüller, A. E.: Deutsche Ztschr. f. Nervenh. **130**:44-60, 1933.

8. Kornmüller, A. E.: Biol. Rev. **10**:383-426, 1935.

9. Adrian, E. D., and Yamagiwa, K.: Brain **58**:323-351, 1935.

10. Jasper, H. H., and Andrews, H. L.: J. Gen. Psychol. **14**:98-126, 1936.

11. (*a*) Fischer, M. H., and Löwenbach, H.: Arch. f. exper. Path. u. Pharmakol. **174**:357-382, 1934. (*b*) Adrian, E. D., and Matthews, B. H. C.: J. Physiol. **81**:440-471, 1934.

One is justified in speaking of the electrical record as the "cortical electrogram," since the potentials originate almost entirely in the gray matter of the cortex. The pattern is practically the same whether one records from the intact scalp, from the underlying periosteum, from the dura or from the outer layers of the cerebral cortex.[12] The pattern alters when one enters the white matter or if the cortex is killed by local heating. The latter experiment was performed on animals by Dusser de Barenne and McCulloch.[13] The statements assume that distant muscle potentials and the electrocardiogram are eliminated by suitable placement of the reference or "average" electrode, for instance, on the lobes of the ears or as a crown surrounding the skull. Local muscle action potentials from the frontalis muscle or the muscles of the jaw are sometimes seen but may be recognized by their characteristic sharp spikes and high, irregular frequencies. With a cooperative subject there is no practical difficulty, and with special precautions a successful record may be obtained even during the convulsion of grand mal epilepsy.[14]

The pattern and degree of cortical activity may be modified by various physiologic and psychologic states. The 10 a second (alpha) rhythm may be considered first. It is best seen when the subject sits or lies quietly, with the eyes closed and the mind at ease. In some persons it runs almost continuously, without varying in frequency more than 2 or 3 per cent, but it usually slows by from 5 to 10 per cent during the second or third hour of a long experiment.[15] Like the heart beat and other biologic rhythms, it is accelerated by a rise in temperature, such as that in fever or diathermy.[16] Unlike the heart beat, it is interrupted or practically suppressed every few seconds, often with considerable regularity. It is more or less completely suppressed, temporarily at least, by opening the eyes, but often it returns even with the eyes open. Apprehension or nervousness may prevent its appearance, and any stimulus that startles the subject or particularly attracts his attention may cause a temporary depression of the alpha rhythm. Concentrated mental effort, such as the solving of a rather difficult problem in mental arithmetic, particularly if there is an emotional element of hurry or embarrassment, may suppress it. Drowsi-

12. Kornmüller, A. E.: J. f. Psychol. u. Neurol. **45**:172-184, 1933.

13. Dusser de Barenne, J. G., and McCulloch, W. S.: Am. J. Physiol. **114**: 692-694, 1936.

14. Gibbs, F. A.; Davis, H., and Lennox, W. G.: The Electro-Encephalogram in Epilepsy and in Conditions of Impaired Consciousness, Arch. Neurol. & Psychiat. **34**:1133-1148 (Dec.) 1935.

15. Loomis, A. L.; Harvey, E. N., and Hobart, G.: Science **83**:239-241, 1936; J. Exper. Psychol. **19**:249-279, 1936.

16. Hoagland, H.: Science **83**:84-85, 1936.

ness, on the other hand, may cause the waves to become slower, larger and less regular in shape and rhythm. These are the typical effects seen in most subjects, but individuals vary widely in the lability of the alpha rhythms.

The 25 a second (beta) rhythm is less labile than the 10 a second rhythm but may sometimes be modified by a sudden, startling stimulus [10] or by sounds. We have seen instances in which musical tones, as well as vision, initiated this rhythm and others in which they abolished it, but these reactions are relatively rare.

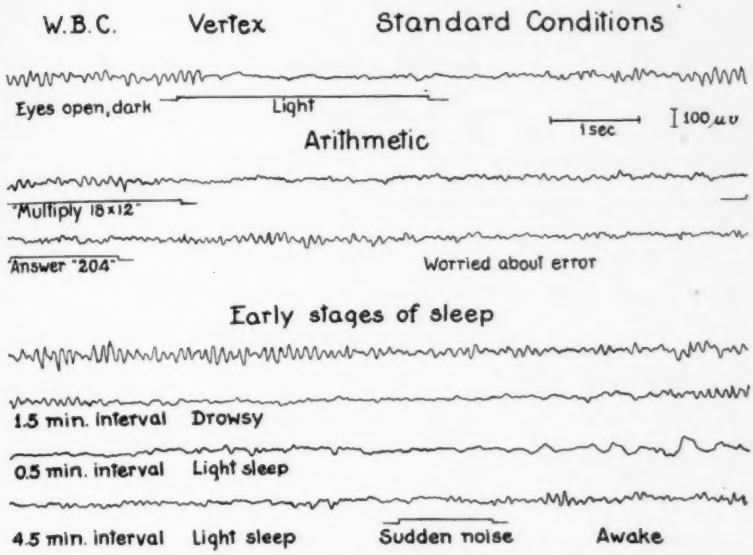

Fig. 1.—Cortical electrograms of a normal man aged 64, recorded from the midline of the occiput, about 2 cm. above the inion. In obtaining this record and the records shown in the other figures the "average" or reference electrode was a pair of plates attached to the lobes of the ears and connected in parallel to the ground. Calibrations of time and sensitivity are given below the first record for one second and 100 microvolts. This subject showed a dominant alpha rhythm, suppressed by illumination. A problem in arithmetic was given at the beginning of the second record. The third record is continuous with the second. The subject later reported considerable worry on realizing the error in his answer a few seconds after giving it. In the records taken during sleep the suppression of the alpha rhythm is followed by the appearance of large, slow waves at the right of the next to the last sample. The interval between the first and second samples is given below the second sample, and so on.

The relation of the cortical electrogram to certain special states and conditions deserves mention. During sleep the 10 a second rhythm disappears at first and is usually replaced by larger, slower and irregular

waves. As sleep continues, the whole activity may be considerably depressed, or at another time it may approach the waking pattern once more. Sometimes a new frequency, of about 14 waves a second, appears for brief intervals. The record during sleep may be quite as variable and complex as that during waking and may be modified by stimuli which do not awaken the sleeper.[17]

Unconsciousness in general, whether from early sleep, cerebral anemia, fainting or anesthesia, seems to be associated with larger and slower waves than the conscious state. Broadly speaking, the deeper the anesthesia the slower the waves,[11b] although ether anesthesia in animals gives a characteristic pattern of small rapid waves.[18]

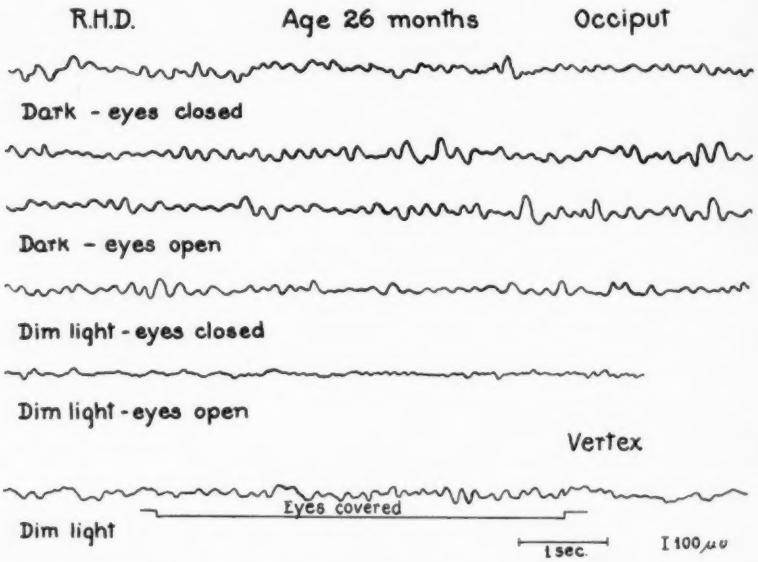

Fig. 2.—Slow alpha waves characteristic of early childhood in a boy aged 26 months. Fairly regular waves with frequencies of from 5 to 7 per second appear, which are slower than those of the normal adult. They appear in darkness or when the eyes are closed or covered but are largely suppressed when the eyes are open in light.

Age appears to be a factor, in that babies under 6 months give large random waves rather than regular rhythms. Regular rhythms of about 4 waves a second begin to appear at about 6 months. The frequency increases progressively to 7 or 8 waves a second in childhood, and the adult pattern and frequency are fairly well established by 10 or 12 years. These statements are tentative, as they are based on a relatively

17. Loomis, A. L.; Harvey, E. N., and Hobart, G.: Science **82**:198-200, 1935.

18. Derbyshire, A. J.; Rempel, B.; Forbes, A., and Lambert, E. F.: Am. J. Physiol. **116**:577-596, 1936.

small number of cases, studied by Dr. D. B. Lindsley.[19] To what extent the random pattern of infancy may be related to that of sleep and unconsciousness is an interesting question.

The age factor seems to be chronological rather than mental age. No relation has yet been reported between the characteristics of the cortical electrogram and mental age or intelligence.

There is no clear evidence of any relation to sex.

The variability and individuality of the records obtained under standard conditions in normal subjects reveal points of fundamental importance. We undertook to study this question in order to establish norms with which to compare records obtained in pathologic conditions.

TECHNIC

For simplicity, we established certain standard conditions. The subject must be awake but lying quietly with the eyes closed and the mind at rest. This implies physical comfort, confidence in the experimenter and freedom from apprehension. Reference, or, as we say, "average," electrodes are connected in parallel to the lobes of the ears and "active" electrodes to the top of the head and to a point just above the occipital protuberance on the midline. The positions correspond roughly to the motor and the visual cortex, respectively, but, admittedly, are arbitrary—as much as are the positions of leads I and II for the electrocardiogram. The electrodes are small metal plates held in place with electrode paste (Sanborn) and collodion. The activity from first one and then the other region is recorded.

RESULTS

Under our standard conditions, a given person reproduces on successive tests his own type of record, which may be characterized by:

1. The presence or absence of a regular alpha (or Berger) rhythm.

2. The frequency of this rhythm, if present. Throughout this paper we have spoken of a 10 a second rhythm. This is the commonest frequency, but in our cases the rhythm ranged from 8 to 13 waves a second. The waves are not considered typical alpha waves unless they show a high degree of regularity and are clearly modified by opening the eyes.

3. The percentage of the time (for a period of at least three minutes) that this rhythm is present. It is almost continuous in some persons. In others the percentage varies considerably from test to test. This lability may be regarded as a characteristic feature.

4. The degree and duration of suppression of the alpha rhythm by standard stimulation, particularly by opening the eyes in darkness, in moderate illumination and in bright light.

5. The prominence of other waves, whether or not of regular frequencies, such as the beta waves. These other waves often appear in the record simultaneously with the alpha waves.

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19. Lindsley, D. B.: Science **84**:354, 1936.

6. The prominence and frequency of the beta waves. These have been designated for brevity as 25 a second waves but their frequency actually ranges from 18 to 50 a second.

7. The general level of activity, which is usually between 20 and 75 microvolts. This is essentially the voltage of an alternating current and has no relation to any measurements which have been reported of the direct current potential of the brain with respect to other organs.

8. Differences between vertex and occipital leads in respect to the points just mentioned.

COMMENT

On the basis of these criteria, different persons show different patterns of activity, but each reproduces his own characteristics. Of course, the individuality is not complete, like that of a finger-print, for the cerebral activity is labile and dynamic and the characterization is essentially statistical.

We studied twenty-three persons on two separate occasions, four on three different days and six on five occasions each. Aside from several instances in which the type of record characteristic of the drowsy state appeared, there have been no exceptions to the rule that a second record taken weeks or months later, but under the same conditions, closely resembles the first. It should be noted that we are comparing not mere brief random samples but in each case a continuous record of from twenty to forty minutes' duration.

It is possible to classify persons in terms of their cortical electrograms. Our initial basis for classification is the alpha rhythm. At one extreme is a very regular, high voltage rhythm, only momentarily interrupted even by opening the eyes. In other instances the alpha rhythm is less continuous, more labile and often mixed with other waves, which may or may not show regular shapes and frequencies. Finally, there is a group of persons in whom the alpha rhythm is rarely visible in the spontaneous record, although it may usually be found for a second or two shortly after the subject has closed his eyes. The records of the latter group usually show low voltage and sometimes slow or random waves or a prominent fast (beta) rhythm. We have classified the first fifty normal adults (from 18 to 64 years, who were not blood relations of one another) from whom we obtained technically satisfactory records under standard conditions at the first session. Of this number, fifteen were women and twenty-three medical or dental students. We divided the records from this group into four classes, according to the estimated percentage of alpha rhythm in at least three minutes of spontaneous records taken under standard conditions. We term alpha rhythms of below 25 per cent "rare," of from 25 to 50

per cent "mixed," of from 50 to 75 per cent "subdominant" and of over 75 per cent "dominant" (fig. 3). Our subjects were grouped as shown in the table.

The accompanying table shows that the subjects in our group were fairly evenly distributed with respect to the rarity or dominance of the alpha rhythm. Furthermore, there was a fairly good correlation between the type of rhythm obtained from the occiput and that from the vertex in this respect. A subject with a dominant or subdominant alpha rhythm at the occiput almost always shows a prominent alpha rhythm at the vertex also and vice versa, but the correlation is by no means perfect. We have refrained from calculating a correlation coefficient, as we do not believe that our estimates of percentages are sufficiently accurate to warrant such refinements. Much more reliable estimates can be obtained by means of an amplifier tuned to respond only to waves of particular frequency, as was recently pointed out by Loomis and his collaborators,[15] and our present figures must be regarded as merely tentative. Their general trend, however, is in accord with the experience and impressions of most other workers in the field with whom we have had the opportunity of discussing the question and is further confirmed by the records of the other sixty persons we have studied.[20]

Distribution with Respect to the Alpha Rhythm of the First Fifty Normal Adults, Not Blood Relatives, Tested Under Standard Conditions

	Type of Alpha Rhythm†	Occiput: Rare	Occiput: Mixed	Occiput: Subdominant	Occiput: Dominant	Total Number of Records from Vertex
Vertex	Dominant	0	0	0	2**	2
	Subdominant	0	1*	8*	5*	14
	Mixed	1	6**	6	3	16
	Rare	8	6	2	2*	18
	Total number of records from occiput	9	13	16	12	

* Positions of the various pairs of identical twins in this classification. Only one twin of each pair is counted in the normal series, but the other twin would fall in the same category in every instance.

** Two pairs of twins fall in this category.

† The basis of classification is the percentage of at least three minutes of spontaneous record (obtained with the eyes closed) which is occupied by the alpha rhythm. Rare alpha rhythms are those of from 0 to 25 per cent; mixed, those of from 25 to 50 per cent; subdominant, those of from 50 to 75 per cent, and dominant, thos of over 75 per cent (fig. 3).

Do these groups represent mere random differences, or do they follow some biologic law? To answer this question we studied eight pairs of identical twins (from 18 to 58 years old). We found that

20. Since this paper was written we have tested fifty additional normal adults, using Loomis' tuned amplifier method. Their distribution according to alpha waves taken from the occiput was: rare, 16; mixed, 8; subdominant, 18, and dominant, 8.

identical twins show similar patterns. The records from one twin resemble those from the other as closely as the records of the same person on successive tests. It is particularly significant that in two instances both members of a pair of twins showed a feature which is unique in our entire series of over a hundred and forty records. In one instance this was an alpha rhythm of 13 per second—the fastest we have recorded. In another case it was an unusual mixture of frequencies, with a different rhythm dominating at the vertex from that found at

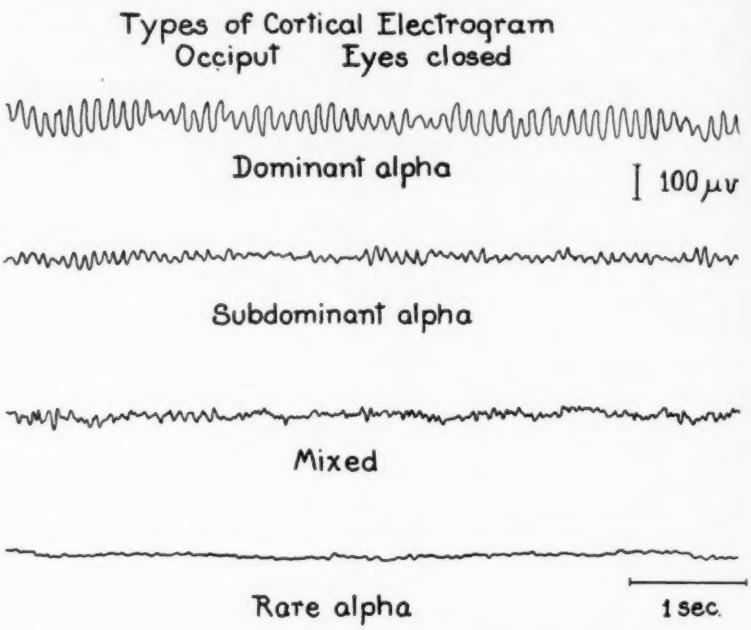

Fig. 3.—Types of cortical electrograms taken under standard conditions from four normal subjects (subjects *D-91, 89* and *88* were men students, aged 22, 23 and 23, respectively, and *D-122,* a woman aged 34). The voltage of the dominant alpha record is much higher than the average.

the occiput. Another unusual feature was the relation between the vertex and the occiput in these same pairs. In both members of one pair the alpha rhythm was mixed at the occiput and subdominant at the vertex, while in the other pair it was dominant at the occiput and rare at the vertex. One of these combinations was unique in the series, and the other was found in only one other instance. In the table the positions of the pairs of twins are indicated by asterisks. One member only of each pair was included in the series, but his twin falls in the same classification in every instance. The odds against these similarities being chance coincidences are overwhelming.

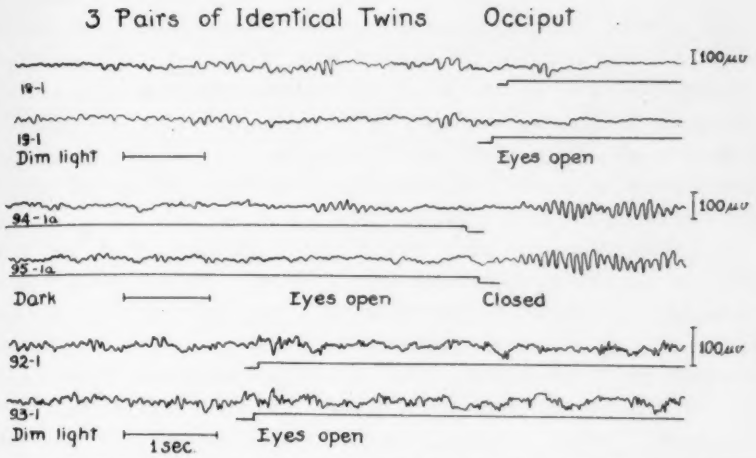

Fig. 4.—Electrograms taken from the occipital region of three pairs of identical twins. They show mixed, dominant and mixed alpha waves, respectively. The upper of each pair of records was taken from one twin and the lower from the other, under the same conditions of response to the same test. Subjects *18* and *19* were women aged 25; *94* and *95*, youths aged 18, and *92* and *93*, men aged 30.

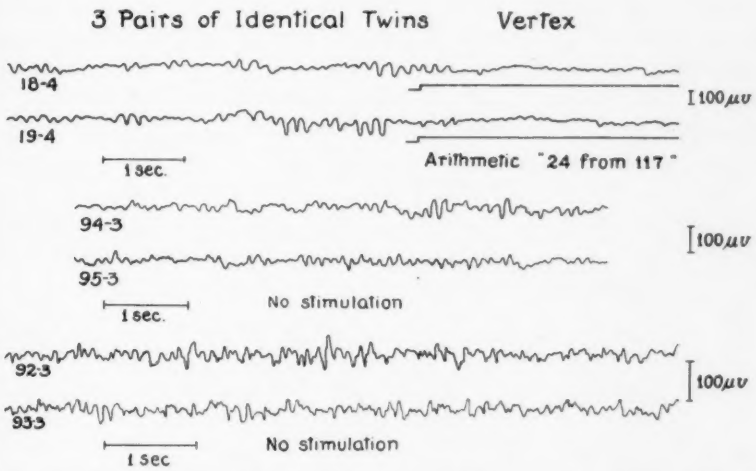

Fig. 5.—Electrograms taken from the vertex of the same three pairs of identical twins as those whose records are shown in figure 4. They show subdominant, dominant and mixed alpha waves, respectively. The response to the arithmetic problem shown by subjects *18* and *19* is the immediate effect of focusing the attention on the command rather than the effect of solving the problem, which appeared a few seconds later in the original records.

CONCLUSION

The cortical electrogram reveals some inborn feature or pattern of cerebral activity. The pattern is labile, to be sure, but the degree of lability seems to be one of its inborn characteristics. The cortical electrogram apparently conforms to the biologic law of similarity of identical twins. How much broader the law may be we do not yet know. Is this an organic, hereditary characteristic? We are at present gathering further evidence on this point.

We think that we have raised more questions than we have answered. At first we asked ourselves: What is the physiologic significance of a spontaneous cortical rhythm, and why should increased activity, such as in vision, apparently reduce it? To what extent may these patterns of activity be related to anatomic areas and known functions? What may the changes in activity tell of the physiologic basis of emotion, of sleep, of attention and of consciousness? Are abnormal patterns to be found in pathologic conditions, either chronic or acute? Most of these questions are still unanswered, and we may now extend the list by asking what the individuality in a record implies. If one is dealing with hereditary patterns and types, with what mental or neurologic characteristics and tendencies may particular cortical electrograms be related? Here is a key, fashioned by physiology out of radio. Has neurology a lock which the key can open?

THE ELECTRO-ENCEPHALOGRAM IN DIAGNOSIS AND IN LOCALIZATION OF EPILEPTIC SEIZURES

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AND

ERNA L. GIBBS

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Many new instruments and technics have been marshaled to the attack on the problem of epilepsy, but each in turn has proved a disappointment. High power microscopes, penetrating roentgen rays and complicated chemical analyses have revealed some of the abnormalities associated with or resulting from seizures, but never the central vital phenomenon: the abnormal functioning of the cerebral neurons. Hopeful as were the prospects when work on epilepsy with modern laboratory technic was first undertaken, there was no definite prospect of foretelling the approach of a seizure or of ascertaining its point of origin in the brain, the manner of its spread or the conditions which alter the abnormal activity of the brain. No technic (laboratory or clinical) could be presumed to diagnose an epileptic seizure in the absence of subjective symptoms or disturbances of behavior. Some of these things which were not even hoped for have now been attained, and progress is being made toward achievement of the others. The technic which has made this possible is the recording of fluctuations in electric potential from the brain.

Berger,[1] when he began his investigations in 1929, was impressed with the variations from the normal electrical activity which he saw in persons with epilepsy, and Kornmüller,[2] working with animals, early

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This investigation was aided by a grant from the Josiah Macy Jr. Foundation.

From the Department of Neurology, Harvard University Medical School and the Neurological Unit of the Boston City Hospital.

Read before the Section on Nervous and Mental Diseases at the Eighty-Seventh Annual Session of the American Medical Association, Kansas City, Mo., May 14, 1936.

1. Berger, H.: Ueber das Elektrenkephalogramm des Menschen, Arch. f. Psychiat. **97**:6, 1932.

2. Kornmüller, A. E.: Der Mechanismus des epileptischen Anfalles auf Grund bioelektrischer Untersuchungen am Zentralnervensystem, Fortschr. d. Neurol., Psychiat. **7**:391 (Sept.); 414 (Oct.) 1935.

noted the large fluctuations in potential which occurred with a seizure induced by overventilation. These Kornmüller called convulsion currents (*Krampfströme*). Recently he published an extremely valuable paper [2] dealing at length with brain potentials during seizures. His work has been on rabbits having both spontaneous and induced seizures. Fischer [3] reported the changes produced by various convulsant drugs on the brain potentials of rabbits.

PETIT MAL PATTERNS

In beginning our work in this field we turned our attention to petit mal epilepsy and found that an extraordinary alteration in brain potentials occurs in this condition. A second or less before the clinical onset of petit mal the usual small and fairly rapid fluctuations that can be led off the brain suddenly disappear and are replaced by a large, approximately sinusoidal wave, followed by a rapid negative deflection (figs. 1 and 2). This formation is repeated about three times a second. The pattern persists as long as the seizure. The swing in voltage during a petit mal seizure may be as much as a millivolt, that is, from ten to twenty times the swing which occurs normally.

These bursts of abnormal electrical activity may occur without objective or subjective evidence of a seizure, but when such is the case, the voltage is usually lower than in the clinically recognizable seizure and the duration of the disturbance is only a second or two. Such subthreshold or larval seizures are scattered in profusion through many of our records. Our first report [4] of this observation was published in collaboration with Dr. Hallowell Davis. We now have electroencephalographic records of fifty-five patients obtained during a petit mal seizure, all of which show this fundamental pattern or some variation of it. Neither Dr. Davis nor Dr. Kreezer has seen this pattern in any of his records, nor have we seen it in records of patients with other neurologic conditions.

Most of these fifty-five patients were known to have frequent attacks of petit mal. Several had a history of petit mal but were thought to be free from it at the time of observation. In a few cases our records furnished the first evidence of the existence of this condition. On the other hand, we have never seen a definite clinical petit mal seizure without the coincident appearance of the characteristic pattern.

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3. Fischer, M. H.: Elektrobiologische Auswirkung von Krampfgiften am zentralen Nervensystem, Med. Klin. **29**:15, 1933.

4. Gibbs, F. A.; Davis, H., and Lennox, W. G.: The Electro-Encephalogram in Epilepsy and in Conditions of Impaired Consciousness, Arch. Neurol. & Psychiat. **34**:1133 (Dec.) 1935.

PATTERNS FROM DIFFERENT AREAS

Our first reports [4] were based on the records made with standard leads from the lobe of the ear and the vertex of the head. The work of Adrian [5] and of Jasper [6] has shown that different types of activity can be obtained from different parts of the head. In normal subjects the large 10 a second wave usually appears best when the active electrode is placed over the occiput and a faster wave, with a frequency of from 14

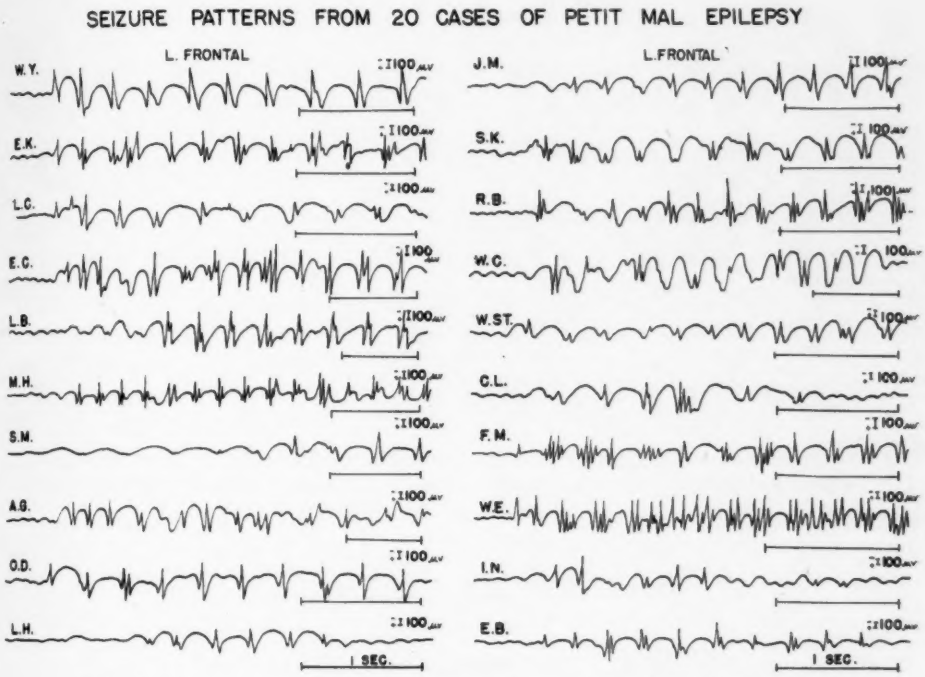

Fig. 1.—Seizure patterns from twenty patients with petit mal epilepsy. All the records show the activity of the left frontal area. Wave and spike formations are obvious in all cases. The duration of the wave and spike formation tends to be about one third of a second, though it is faster at the start of the seizure and slower at the end. The relatively flat tracing at the left of each record is the patient's normal record. These records and those in the accompanying figures unless otherwise stated, were made with one lead to the lobe of the ear and the other to the area designated, the electrode to the ear being connected to the ground of a capacity-coupled amplifier and the other to the grid. The recording instrument was in each case an ink-writing galvanometer. In all records an upward deflection indicates that the electrode connected to the grid was negative with respect to the ear. The calibration in microvolts is given at the end of the record. The horizontal line in the lower right corner marks the duration of one second.

5. Adrian, E. D., and Yamagiwa, K.: The Origin of the Berger Rhythm, Brain **58**:323, 1935.

6. Jasper, H. H.: Cortical Excitatory State and Variability in Human Brain Rhythms, Science **83**:259 (March) 1936.

to 20 a second, can be best obtained as a rule with the active electrode over the frontal region. This is in rough agreement with the work of Kornmüller on the rabbit, showing that a certain type of record is obtained from a certain architectonic field. Likewise, our petit mal seizure records vary with the area of the cortex over which the active

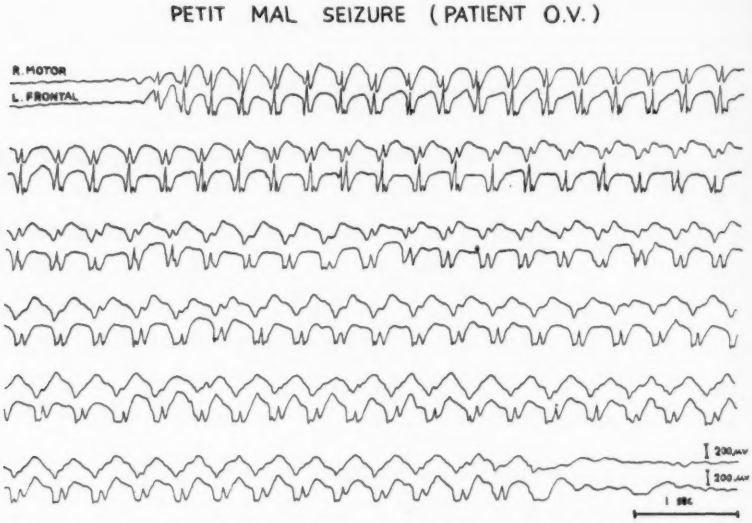

Fig. 2.—Records showing the electrical activity of the brain before and during a petit mal seizure. The records were taken simultaneously from the right motor and the left frontal area. No interval occurred between the strips.

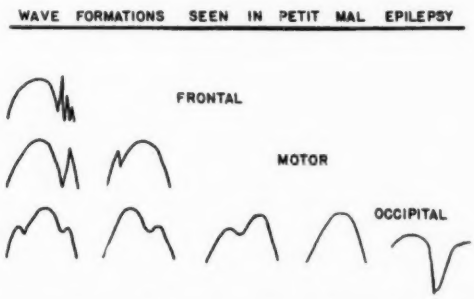

Fig. 3.—Wave formations which appear in petit mal epilepsy. The wave and multiple spike pattern appears most often in records taken from the frontal area, and the wave and small spike of long duration, in records taken from the motor area. The other formations are most frequently seen in records taken from the occipital area.

electrode is placed. The formations which appear with different leads are shown in figure 3. The wave and spike pattern is seen best in the

frontal region, and the wave and hump formation in the occipital area. Over the motor region one usually obtains a lower voltage disturbance, with a rather flat-topped wave and small spike. The spike has a wavelength such that if repeated to form a continuous pattern it would have a frequency of from 15 to 20 per second, and if the hump repeated to form a continuous pattern it would have a frequency of about 10 per second. This suggests that the wavelength or frequency of the fast components of the petit mal formation is determined by the wavelength or frequency which is normal for the underlying cortex.

Our investigation early began to center around the question of the origin of this pathologic electrical activity. By making simultaneous

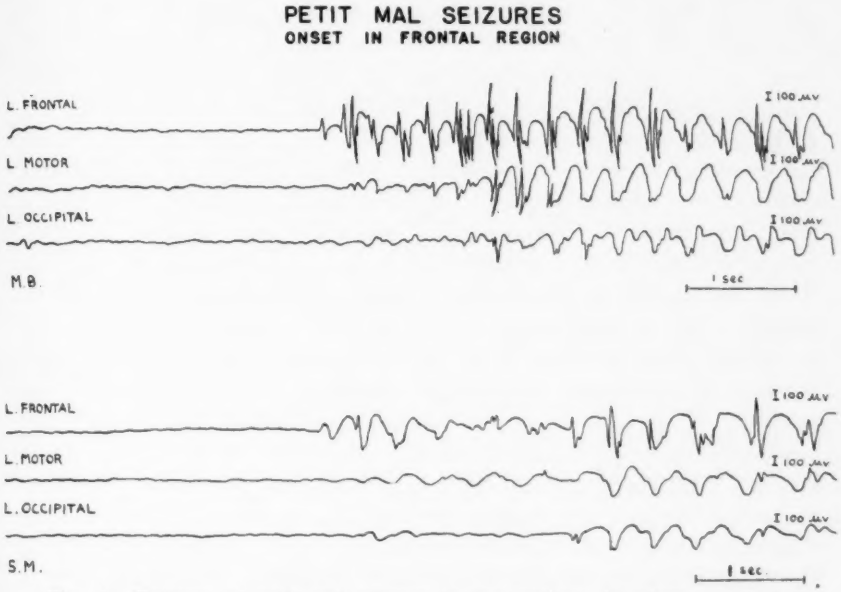

Fig. 4.—Patterns of petit mal seizures in two patients in whom onset of the disturbance in the frontal area preceded that in the motor and occipital areas. The method of recording, etc., is described in the legend for figure 1.

records from different parts of the brain we determined that the greatest fluctuations in voltage in petit mal seizures usually appear in the frontal region and that when one part of the brain definitely precedes all others in showing the pathologic activity the frontal lobe is usually first involved (fig. 4). The pathologic activity may, however, show an apparently simultaneous onset in all cortical areas (fig. 2) or, more usually, in both frontal areas. It is true also that some other area of the cortex may appear to lead all others; i. e., an apparent motor or occipital onset may be seen. These facts suggest that the frontal areas

do not originate the disturbance but that they are more closely linked with the source of the disturbance than any other cortical area that we have investigated. It is noteworthy in this connection that when larval petit mal seizures involve one area alone it is most commonly the frontal area. The activity in the frontal and occipital lobes is often 180 degrees out of phase; that is, the record from the frontal area may show a negative spike or wave while that from the occipital region shows a positive wave. This is not necessarily so, for in the same seizure the activity may at the outset be in phase in all areas and become out of phase only as the seizure progresses. We studied a case in which the wave and spike pattern occurred every few seconds during sleep and was confined entirely to the frontal lobe. The boundary between the zone of pathologic and that of normal activity could be clearly made out. Over the boundary zone the movement of the electrode 1 cm. toward or away from the pathologically active area altered the record greatly. The cortex of both frontal regions, however, showed bursts of the wave and spike pattern, sometimes synchronously, sometimes slightly out of phase and sometimes independently. Neither side consistently led the other. After operative removal of the atrophic tip of the right frontal lobe, independent abnormal activity was no longer obtained from the right side. Studies of this kind lead us to believe that in patients in whom the disturbance begins in a certain portion of the cortex our technic is adequate for localization.

When we began the present investigation we were doubtful whether Kornmüller's work on rabbits was applicable to the study of human epilepsy. In his recent paper, however, he showed records of spontaneous seizures in rabbits which look like those we have obtained in attacks of petit mal, and he noted that during the tremendous electrical discharges recorded the animal showed little in the way of convulsive movements. The close similarity between our records and those of Kornmüller can be seen by referring to figure 5. We conclude that rabbits are subject to petit mal seizures. It may be possible to find the source of these seizures in the rabbit and to use this information for an understanding of the condition in man.

The appearance of the petit mal waves is so peculiar and their voltage so high that we considered the possibility that the basic disturbance was essentially electrical. In order to test this possibility we put back into the brain waves of the same shape as those which accompanied the seizure, with the same and higher voltages. In no case, however, were we able to precipitate a seizure. It is likely that the abnormal waves obtained in a seizure bear the same relation to the abnormal function of the brain that the abnormal electrocardiogram bears to heart block, and we may have been as foolish in attempting to produce a petit mal seizure by applying these voltages to the brain as we

would if we attempted to produce heart block by shocking the heart with the type of voltage obtained in that disorder.

GRAND MAL PATTERNS

We have said most about patterns in petit mal because this is the type of seizure which we have studied most. On the basis of clinical and electrical evidence, moreover, we consider that petit mal and grand mal are closely related disorders and that they rest on the same pathologic foundation. We have occasionally seen grand mal seizures start with a burst of petit mal waves and end with what might be described as petit mal status. We have seen a petit mal seizure initiated by what electrically appeared to be the beginning of a grand mal seizure. An hour later a grand mal seizure occurred, the first that this patient had had for several weeks.

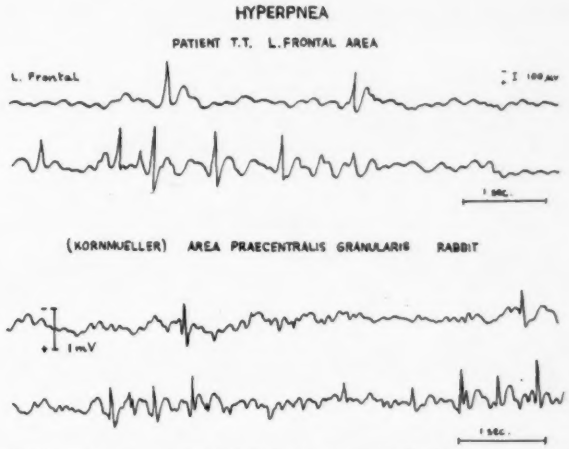

Fig. 5.—Petit mal waves precipitated by overventilation of a patient, compared with part of Kornmüller's record of *Krampfströme* (seizure currents) obtained by the same procedure in the rabbit. There was no time interval between the strips, which represent a single lead.

In an attempt to study grand mal one is faced with the difficulty that these convulsions occur more infrequently and are accompanied by such violent movements that rigid fixation of electrodes is difficult, large muscle action potentials may be introduced, and static charges, due to sliding of the body about on the bed or shifting of the resistance to the ground, causes troublesome artefacts. All these difficulties, however, with patience and care may be overcome. The type of disturbance which appears in grand mal is shown in figure 6.

In all cases, in the early part of the seizure there is a relatively fast wave, with a frequency of from 10 to 30 a second, which increases in

voltage as the seizure progresses. These waves tend to clump together and to be interrupted usually as the clonic phase sets in. As the clonic phase progresses, slower waves appear, and the fast activity decreases in voltage and becomes much more intermittent. The last clonic jerk is usually accompanied by a feeble outburst of the fast waves. In general there is good correlation between the predominant frequencies of the slower waves and the rhythm of the muscle jerks. During the postseizure stupor fast activity is absent; either the record appears

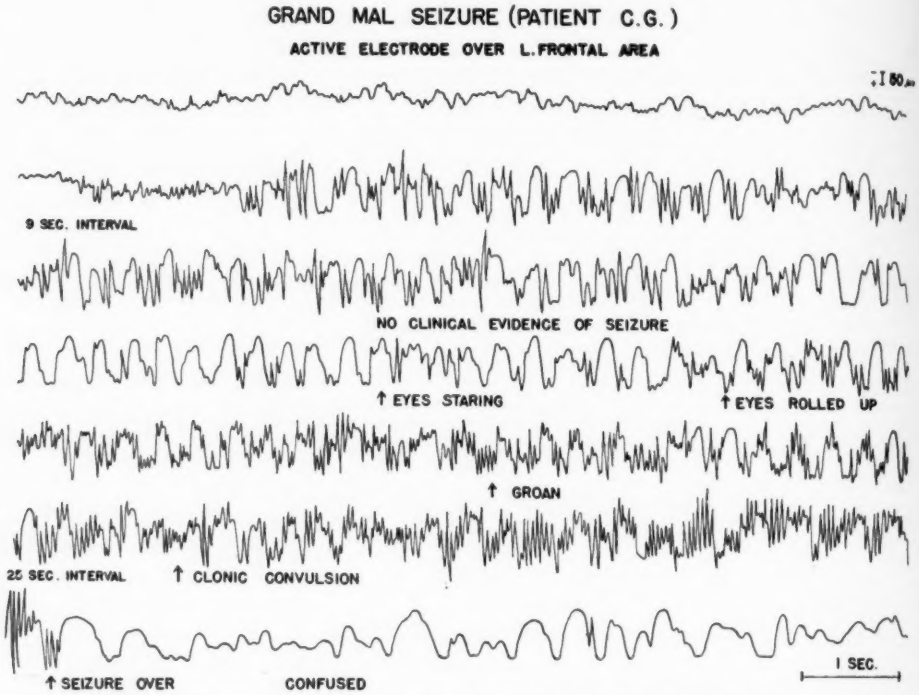

Fig. 6.—Records of the electrical activity of the left frontal area in a grand mal seizure. Obvious changes in the record occurred before either objective or subjective evidence of the seizure. It will be seen that the first change is in the waves with the higher frequencies. With these an increased voltage develops then slower waves appear and with the fast waves suggest at times a petit mal pattern. (This patient also had petit mal seizures.) The first convulsive movements occurred when many fast waves of high voltage appeared. The record is devoid of waves of fast activity when the seizure was over; it shows only large slow waves and an occasional wave and spike formation.

abnormally flat, or, if the patient is confused rather than stuporous, large, slow waves are present. Gradual reappearance of more and faster waves goes step by step with recovery from stupor.

In status, after tracing the course of the electrical activity through a number of seizures it is possible to foretell the next seizure, for it tends to occur as soon as recovery to an approximately normal level of electrical activity has been achieved.

In patients subject to seizures of grand mal, as in patients with attacks of petit mal, we have seen disturbances similar to those observed at the time of the seizure but of lower voltage and shorter duration. These seizures we have called "larval" or "subthreshold." Two examples of such larval grand mal seizures are shown in figure 7.

That the technic we use is adequate for localizing the place of onset of a disturbance of the grand mal type (if it has a localized origin) is indicated by the record shown in figure 8. This patient suffered from jacksonian seizures starting in the right side of the face and spreading to the right (paralyzed) arm and leg. During convulsions the left arm

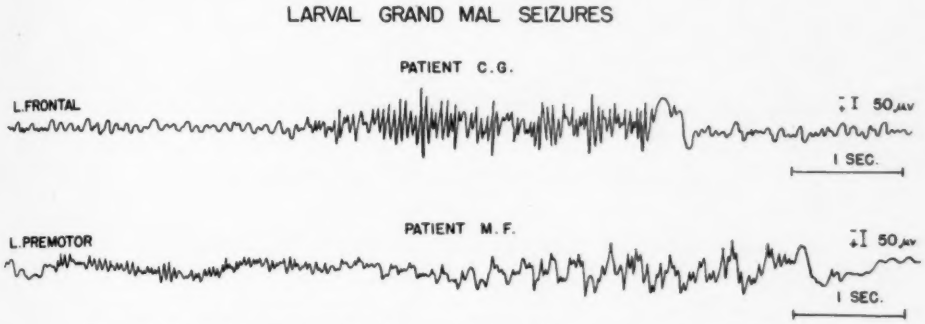

Fig. 7.—Larval grand mal seizure patterns from two patients. The upper tracing is from the patient whose record is shown in figure 6. This larval grand mal seizure and the onset of the grand mal seizure shown in figure 6 are comparable.

The lower record is from a patient in status epilepticus. Clinically obvious seizures occurred about every fifteen minutes and gave records similar to that seen in figure 6. Occasionally a clinically obvious seizure did not occur, and instead of the full-fledged grand mal attack the record showed an abbreviated disturbance, such as is shown in the lower record.

In neither of these subthreshold seizures was there clinical evidence of a disturbance associated with the abnormal discharge.

and leg were limp. Electrodes were attached to corresponding points over the right and left motor areas. The abnormal electrical activity appeared in the record from the left motor region before it appeared in that from the right.

We intend to pursue this type of investigation in the hope of determining the region of origin of these electrical disturbances. We believe that we shall have to investigate regions deeper than the cortex, and

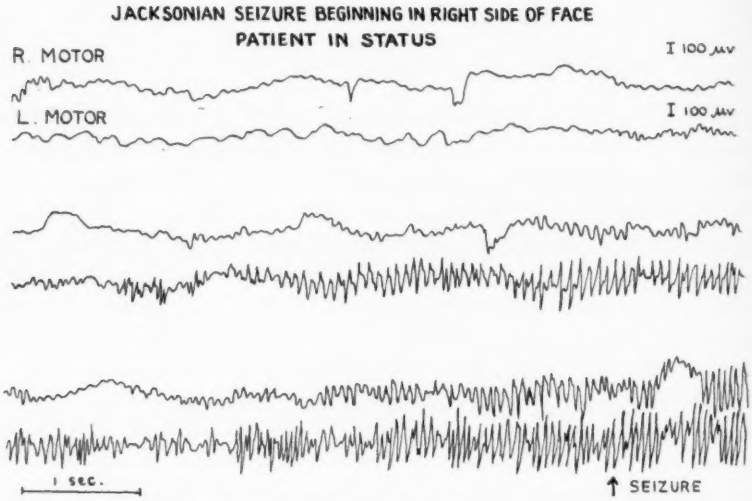

Fig. 8.—Records of the electrical activity of the left and right motor areas during a jacksonian seizure on the right side, starting in the face.

It will be seen that the waves of abnormal voltage appeared first in the left motor area. The preseizure record from the left motor area shows large slow waves, which suggest disturbed activity of the underlying tissue, particularly when compared with the small normal, 10 a second waves obtained from the opposite motor area. The patient had right hemiplegia. During the convulsion the left side was flaccid.

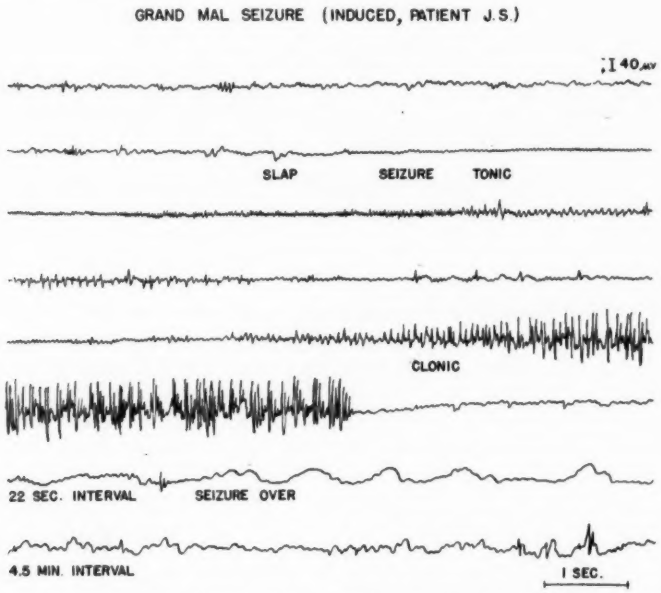

Fig. 9.—Record of electrical activity during a grand mal seizure, made with a pair of concentric needle electrodes in the right motor area. The patient had reflex epilepsy. This seizure was precipitated by a slap on the thigh. The increase and decrease in voltage production during the seizure are probably to be accounted for by the sweeping back and forth of pathologic electrical activity over the brain. With the localized leads used large potentials could appear only when the source of the abnormally high voltage lay close to the tip of the needle. Notations are placed below the curve referred to.

for this purpose we have begun to use needle electrodes thrust directly into the brain. That the use of an electrode of this type gives data which are in accord with those we have obtained with leads from the scalp is indicated in figure 9; this shows a record made with a pair of concentric needle electrodes placed in the parietal region of the brain. The patient into whose brain these electrodes were inserted could be thrown into a convulsion by surprise. The electrical disturbance which accompanied such an induced seizure is shown in this figure. The increase and decrease in voltage production during the seizure correspond to a shifting of the seizure from one part of the body to another, and both are probably to be accounted for by the sweeping back and forth over the brain of the pathologic activity. With the localized leads used, large potentials could appear only when the abnormal voltage production occurred close to the tip of the needle.

CONCLUSIONS

A 3 a second wave and spike pattern in the electro-encephalogram is pathognomonic of petit mal epilepsy.

The frontal lobe is more intimately connected with the source of the pathologic electrical activity associated with petit mal than any other cortical area accessible from the surface of the head.

The type of pathologic electrical activity tends to be characteristic for the particular cortical area which produces it.

Available technic is adequate for determining the point of origin of a seizure. It should be only a matter of time before there will be an answer to the question: Where do epileptic seizures start?

EFFECT ON THE ELECTRO-ENCEPHALOGRAM OF DRUGS AND CONDITIONS WHICH INFLUENCE SEIZURES

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Of what clinical value is the study of cortical potentials to the physician who must treat patients with epilepsy? Is there hope of clarifying and unifying the confusing and often diametrically opposed advice given by different physicians to these patients? A prime difficulty has been the impossibility of submitting the therapeutic problems to laboratory tests. Convulsive seizures are irregularly spaced; surrounding conditions and bodily states vary from day to day, so that therapeutic trial consumes months or years and conclusions are perilous. Finally, the seizure is only the portion of the tree above the ground, the visible expression of the disturbance in the brain. The electro-encephalogram lays bare the roots. By the use of this technic, utilizing patients with frequent minor disturbances, one can in the laboratory make a running record both of clinical seizures and of the lesser disturbances which give no clinical evidence of their presence. One can induce bodily states which produce types of electrical activity parallel or opposite to the type of activity encountered in seizures. One can, furthermore, study the effect of various drugs on the seizure pattern.

There are, then, two types of evidence which we shall use. The first is of value as a background but furnishes evidence only of a priori and suppositional value, i. e., whether the experimental drug or procedure induces alterations in the pattern of the electro-encephalogram which are similar to those occurring in a seizure. The second type of

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evidence is of direct and full value, i. e., whether the drug or the procedure affects the seizure as it is visualized on the tape.

ATTENTION

In states of mental alertness the action potentials have a lower voltage, and the waves flatten out, which is the antithesis of the magnified potentials always associated with seizures. We are not as yet fortified with a body of observations sufficient to provide statistical evidence, but we have individual records which show suppression of petit mal patterns when the attention is focused. J. M. had abnormal electrical disturbances appearing at intervals of a few seconds. We

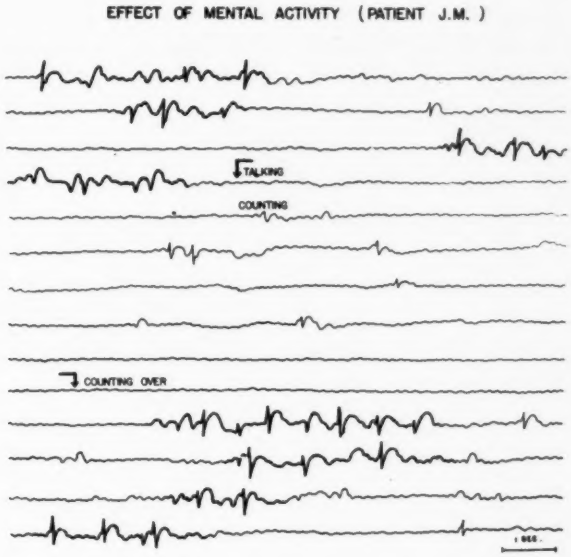

Fig. 1.—Effect of attention on the petit mal seizures of J. M. The record was obtained from the frontal area and is continuous. Between the points marked by large arrows the patient's attention was engaged. The portions of the curves in which prolonged periods of abnormal potentials appear are inked more heavily than the rest of the record. In this figure and in the accompanying figures the period of one second is indicated in the lower right corner.

noticed that while he was speaking the abnormal patterns did not appear on the tape (fig. 1). The patient corroborated this laboratory observation, volunteering the information that when waiting on customers (he was a clerk) he rarely had a petit mal sensation, which he described as an "electricity feeling through the head and arms." In further support of the assertion is the fact, pointed out by Weiss and

Baker [1] and frequently observed by us, that patients with hyperirritability of the carotid sinus lose consciousness with much more difficulty if they are engaged in conversation while pressure is applied to the sinus. Many patients insist that they can fight off an epileptic seizure of which they have warning. Since the time of Galen, many patients with jacksonian epilepsy have found that they can prevent the convulsion from spreading if they twist or rub the extremity which is first affected.

Electrographic and clinical observations are in accord on this point: The mind of the patient with epilepsy can aid his brain. Attentiveness and mental activity, often the victims of epilepsy, are themselves capable of offering active opposition to the appearance of seizures. The practical application seems to be that patients, especially in the early stages, should not be given a prescription calling for idleness and vacancy of mind but should be encouraged to continue in school and business, to seek stimulation and to avoid stagnation.

SLEEP

Sleep and seizures have loss of consciousness in common. From the point of view of the electro-encephalogram, sleep and seizures are analogous disturbances; both are characterized by abnormally great fluctuations in the voltage and variations in the frequency of the rhythms. Of the twenty-four hours, those devoted to sleep hold the record for the number of seizures, a circumstance puzzling to therapeutists who believe in absolute rest as the best treatment for epilepsy. What is the effect of sleep on seizures? Obviously, no general statement can be made, for seizures may occur only during waking, only during sleep or indifferently. Although statistically there appears to be a positive relationship between seizures and sleep, the best anticonvulsants are soporific.

We have seen light sleep and phenobarbital produce much the same changes in the pattern of the petit mal record. In light sleep, however, the pattern between seizures was altered, whereas after the injection of phenobarbital it was normal. In most cases we have studied so far, the petit mal formation did not appear in deep sleep. In such cases sleep seems to be anticonvulsant. Some of the patients, though free from petit mal in deep sleep, showed a series of petit mal seizure waves when drowsy or when waking from sleep. This indicates that certain stages of sleep or the transition from one stage to another can actually activate the seizure mechanism.

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1. Weiss, S., and Baker, J. P.: Carotid Sinus Reflex in Health and Disease: Its Rôle in Causation of Fainting and Convulsions, Medicine **12**:297 (Sept.) 1933.

Other patients, especially those subject to nocturnal convulsions, may have alteration or actual increase of seizure patterns in sleep. One such patient had a history of nocturnal grand mal seizures five or ten times a year and of petit mal attacks as many times a day, but only when he was awake. The petit mal attacks were accompanied by twitching of facial muscles and torsion of the body. When the patient was in deep sleep the electro-encephalographic record showed almost continuous petit mal waves, though the patient himself lay quietly in slumber, without any of the involuntary movements so obvious in his seizures when awake. Furthermore, sleep greatly modified the patient's

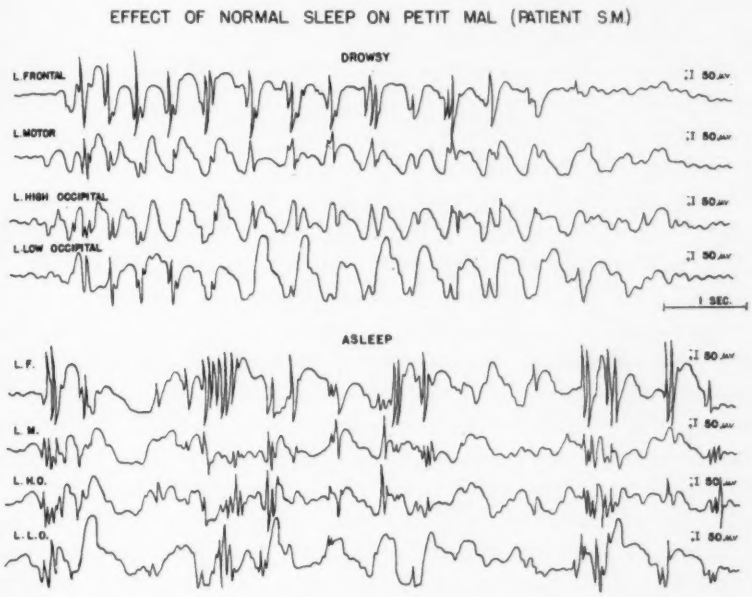

Fig. 2.—Effect of normal sleep on the frequency and form of abnormal potentials. The two sets of curves were taken from four regions of the skull, corresponding to the frontal, motor and high and low occipital areas of the brain. The upper set, taken when the patient, S. M., was awake but drowsy, shows the usual petit mal pattern for this patient, returning to normal at the extreme right of the figure. The attack of petit mal was accompanied by considerable muscular twitching. The lower quartet of curves, taken some minutes later, during sleep, shows the almost continuous abnormality existing during sleep. Although the abnormal electrical activity was even greater than that during a seizure of petit mal while the patient was awake, there was no visible clinical evidence of seizure. In this figure and in the succeeding figures, an upright line at the right of each curve marks the signal given by 50 microvolts.

seizure pattern, with an increase in the number of spikes of negative potential (fig. 2). Another patient had almost continuous abormal activity, not only during normal sleep but during sleep induced by a

barbiturate. Therefore, even in deep sleep, either natural or induced by an antiepileptic sedative, pathologic electrical activity of the brain may occur.

Sleep itself is a mystery, and the problem of epilepsy is not simplified by having to consider the reciprocal relationship of sleep and seizures. The two are intimately bound together, and possibly investigators will have to unravel the mysteries of both in order to understand either. We report in this paper merely the beginning of such an undertaking.

ALTERATIONS IN CARBON DIOXIDE CONTENT

During the past twelve years a variety of conditions which alter the chemical state of the body (acid-base and water balance and oxygen and dextrose concentration) have been shown to influence the frequency of seizures. At this time we shall speak only of the effect of alterations in acid-base balance brought about by decreasing or increasing the carbon dioxide content of the blood.

Voluntary hyperpnea, which "blows off" carbon dioxide from the lungs and blood, results in potentials which are slow and of large voltage. These qualitative changes are the same as those which occur with seizures. Furthermore, in dozens of our patients having frequent attacks of petit mal a moderate amount of hyperpnea produced large, slow waves and after these the patient's characteristic petit mal pattern.[2] On the other hand, inhalation of a mixture of 10 per cent carbon dioxide and 90 per cent oxygen decreases the voltage of the electroencephalograms of normal persons. In the few patients on whom we have made tests, the inhalation of this mixture wiped out the abnormal, spontaneously occurring petit mal waves. An example of this is shown in figure 3. That the carbon dioxide was the effective agent is proved by the fact that inhalation of oxygen had no influence on the frequency of seizures.

DRUGS

We have observed the effect both of convulsant and of anticonvulsant drugs. De Meduna [3] employed camphor as a convulsant in the treatment of a series of patients with schizophrenia and reported beneficial results. We find that from eighteen to twenty seconds after the intravenous injection of a small amount of a preparation of camphor (methylisopropylcycloherone dissolved in an aqueous solution of sodium salicylate), an interval which presumably represents the time required

2. Gibbs, F. A.; Davis, H., and Lennox, W. G.: The Electro-Encephalogram in Epilepsy and in Conditions of Impaired Consciousness, Arch. Neurol. & Psychiat. **34**:1133 (Dec.) 1935.

3. de Meduna, L.: New Methods of Medical Treatment of Schizophrenia, Arch. Neurol. & Psychiat. **35**:361 (Feb.) 1936.

for the blood to circulate from the arm vein to the cells of the cortex, the potentials begin to increase in amplitude. Rapidly the waves become progressively larger and more frequent until a convulsion occurs. In the patient whose record is shown in figure 4, a short but typical petit mal seizure occurred thirty-one seconds after the injection. (This patient had no history of petit mal.) Thirty seconds later convulsive movements began. After the convulsion, for a period of from ten or fifteen minutes, the record was abnormally flat. This record is similar to those obtained in spontaneous seizures of grand mal. The patient

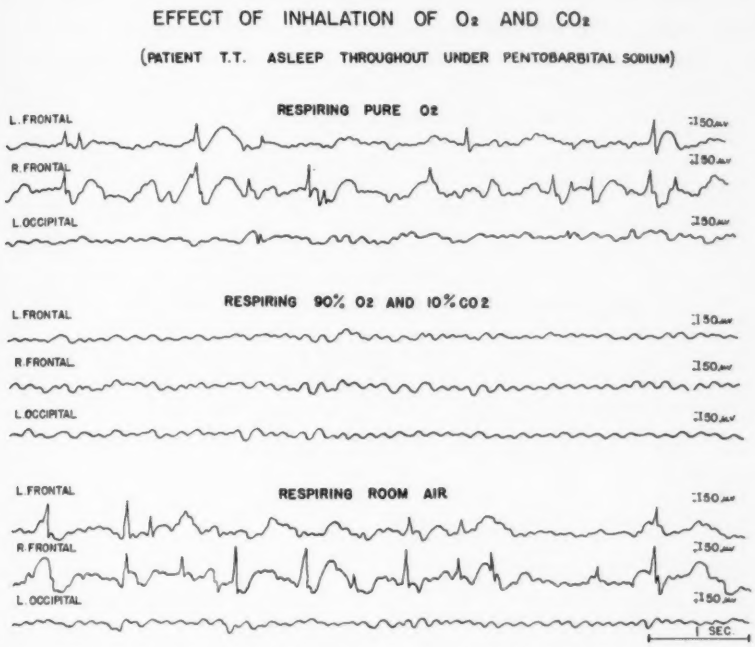

Fig. 3.—Effect of the inhalation of oxygen and carbon dioxide on the electro-encephalogram of T. T. The upper trio of curves was taken while the patient was breathing pure oxygen through a mask. The middle trio is a sample of the record taken while he was breathing a mixture of 90 per cent oxygen and 10 per cent carbon dioxide. The trio at the bottom represents a control period, when he was breathing room air. Throughout the period of observation, the patient was asleep, as a result of intravenous injection of pentobarbital sodium. Practically none of the abnormal sharp spikes were present during the whole period of breathing carbon dioxide.

was apparently unconscious from about the appearance of the petit mal. Afterward he had only the recollection of a sensation of dizziness following the injection of the drug.

Of more clinical interest are the studies dealing with anticonvulsant drugs. For ease of observation, these studies have dealt so far with

minor seizures, which constitute about 70 per cent of all epileptic attacks. We were interested in determining the effect of anticonvulsant drugs on brain potentials in the normal state and also, if possible, the mechanism by which they act as anticonvulsants in persons with epilepsy. Does the drug merely prevent the appearance of the seizure, or does it circumvent or suppress the abnormal disturbance after it starts? Does the drug act on one region of the cortex more than on another?

It should first be remarked that both in patients who have epilepsy and in those who do not phenobarbital and bromide act much like other sedative drugs and, indeed, like normal sleep, in slowing the frequency and increasing the voltage of the normal waves.

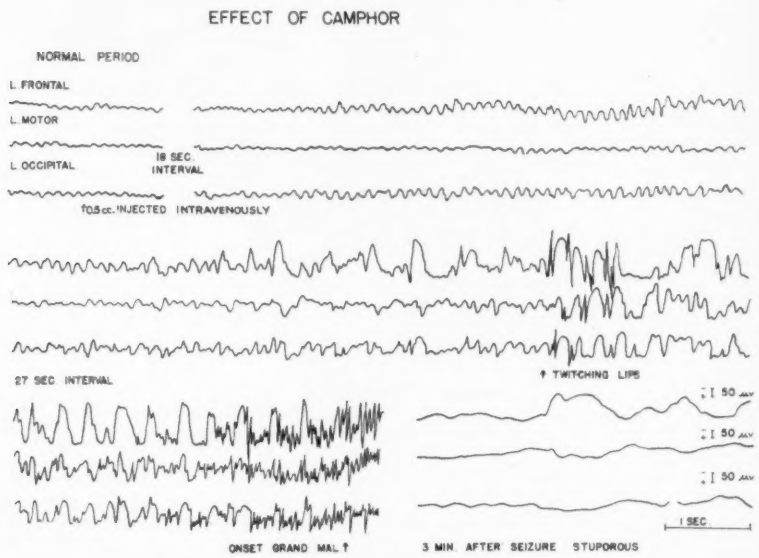

Fig. 4.—Record of the potentials obtained after the intravenous injection of 0.5 cc. of a preparation of camphor. An eighteen second interval separated the record for the normal control period at the left (during which the drug was injected) from the rest of the record. An interval of twenty-seven seconds separated the second trio of curves from the third. After the onset of grand mal attack in the middle of the trio of curves at the bottom, records could not be obtained. A three-minute interval separated the end of the grand mal seizure from the after-period. Near the end of the middle trio of curves is a series of four or five waves which are typical of petit mal. These were accompanied by twitching of the eyelids. The three curves are simultaneous records from the frontal, motor and occipital areas.

After a period of control for observing the frequency of the seizures which were recorded on the tape, as well as the pattern of the waves, we injected intravenously into subjects with epilepsy from 5 to 10 grains

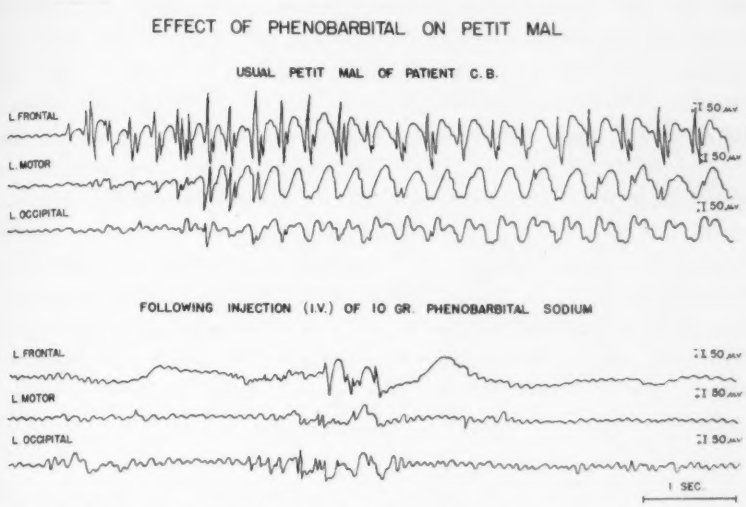

Fig. 5.—Effect of injection of phenobarbital. The upper set of curves is a record of the usual pattern of the potentials during an attack of petit mal in C. B.: The abnormality appeared in the lead from the frontal region a second or two before it appeared in that from the motor or occipital area. Below is a record of the type of electrical disturbances which occurred in this patient after an injection of phenobarbital sodium.

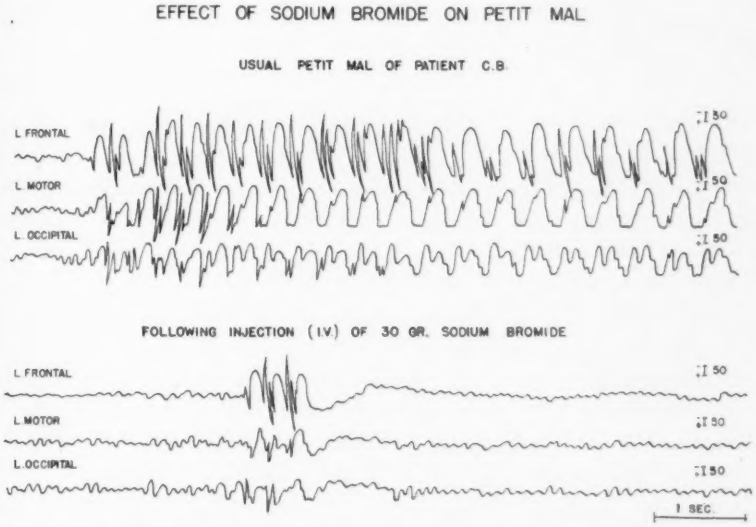

Fig. 6.—Effect of injection of sodium bromide on petit mal. The record was taken from the same patient for whom tracings are shown in figure 5, and the experiment followed the same procedure, except that 30 grains (1.94 Gm.) of sodium bromide was injected intravenously.

(0.324 to 0.648 Gm.) of phenobarbital sodium or 30 grains (1.944 Gm.) of sodium bromide and watched the tape for the effect on the abnormal complexes. We observed that administration of these drugs acted in two ways. First, the interval between seizure patterns was greatly prolonged, and, second, when the seizure pattern did appear it was short and distorted. In the upper portion of figure 5 is one of the patient's usual petit mal patterns. Below is a sample of the complex which appeared after injection of phenobarbital. The seizure started as usual, but after one second it became disorganized into a jumble of large slow waves. The usual rhythm was resumed without either the patient or the observer being aware that anything had been amiss. In other words, for a period after a single large dose of the drug all seizures become subthreshold, recognized only by the electro-encephalogram.

Proportion of Time in Which There Was Abnormal Cortical Activity in Patient J. M.

Procedure	Length of Period, Min.	Proportion of Period in Which Record Was Abnormal, Percentage
Lying quietly (control period)	5.5	24.0
During and shortly after hyperpnea	2.8	41.0
During and after breathing nitrogen	0.6	31.0
During talking and counting	0.8	5.3
During and after breathing 10% carbon dioxide and 90% oxygen	2.8	0.0
After injection of 10 grains of phenobarbital	20.9	0.1
Typical petit mal (10 min. later)	11.1	3.2
Atypical petit mal (same period)	....	8.2
Total period of abnormal waves (same period)	....	11.4

The effect of sodium bromide on the petit mal waves of another patient is shown in figure 6. The general effect seems to be about the same as that obtained with phenobarbital. The question as to whether bromides and phenobarbital present differences of detail in their action will require further study.

These drugs influenced the size and shape of the waves from all areas from which the potentials were led off. There was no indication in the patients so far studied that the cortex in one area is influenced more than that in another. However, the question of localization of the specific action of the anticonvulsant drugs requires further research, which should not be confined to studies of its action on the cortex.

In order to compare numerically the effects of the various procedures which have been named, we computed the proportion of the electro-encephalogram in which the rhythm was abnormal. The results for the patient J. M. appear in the table. In a control period when the patient was lying quietly with the eyes closed, abnormal potentials were obtained from the frontal area 24 per cent of the time. Various

procedures were tried successively, after each of which time was given for the frequency of the petit mal waves to return to that for the "resting" state. Two minutes of voluntary overventilation and half a minute of breathing nitrogen caused a definite increase in abnormal waves, while attention, breathing 10 per cent carbon dioxide and injection of phenobarbital temporarily, or nearly, abolished them.

CONCLUSIONS

Certain conditions which alter the electrical activity of the cortex of normal subjects alter also the pathologic electrical activity which is associated with epileptic seizures. Attention and the inhalation of carbon dioxide, both of which decrease the fluctuations in voltage of potentials from the normal cortex, tend to prevent the appearance of petit mal waves. Sleep, which is characterized by bursts of great fluctuation in voltage interspersed with periods of flatness, seems at times to cause and at times to prevent pathologic activity. The effect seems to depend on the depth of sleep and on individual differences in patients. Overventilation, which causes large, slow voltage fluctuations in normal subjects, tends to precipitate seizures in persons with epilepsy.

Phenobarbital and sodium bromide prevent or alter the pathologic activity associated with a seizure. In doses which are not sufficiently large to modify the electrical activity during normal periods these drugs prevent or modify the electrical activity associated with a petit mal seizure.

Because the electro-encephalogram permits recording of the electrical disturbance in the brain which is the epileptic seizure, the technic is an aid not only in the better understanding of epilepsy but in the evaluation of various means of treatment.

ABSTRACT OF DISCUSSION

On Papers by Kreezer; Davis and Davis; Gibbs, Lennox and Gibbs, and Lennox, Gibbs and Gibbs

Dr. L. E. Travis, Iowa City: The essayists have been so cautious in their statements that a reviewer has difficulty in finding an opening. However, I should like to carry this conservatism and modesty still further. Dr. Kreezer and Dr. Davis discussed the concept of alpha and beta waves, implying a bimodal distribution of brain potentials, as to both frequency and extent. I think that this might be questioned. It might be wiser, temporarily at least, to consider brain potentials as ranging in frequency from such rates as 2 or 3 waves per second up to 20 or 25 or even 50 waves per second, without trying to read into the record two different kinds of waves. If one should read all potential waves and plot them according to both frequency and intensity, one would get, according to the analyses made by my associates and me, practically a normal curve for distribution in regard to both these aspects.

I should like to see Dr. Kreezer and Dr. Davis do this: Let them take four records from each of a number of subjects at different times and under the same conditions. Then let these records be mixed and given to some one who is familiar with brain potential records and see whether he can classify them into groups that are somewhat similar to the groups that the experimenter who knows the waves and knows the subjects might be able to arrange. Possibly they have done that. This might be a good check.

Dr. Kreezer reported the following figures: 52 per cent of regular sequences for persons of a certain level of mentality, 48 per cent for those of another level, 21 per cent for those of a third level and 19 per cent for those of a fourth. I suspect that there would be no difference between 48 and 52 per cent and no significant difference between 19 and 21 per cent; there might be a difference between 21 and 48 per cent. I suppose that Dr. Kreezer has the statistical values for these differences, and possibly they are statistically significant. I think that they ought to be checked.

I was interested in the report by Dr. F. A. Gibbs, Dr. Lennox and Dr. E. L. Gibbs in regard to so-called abnormal potentials. I wish to raise two questions. I asked Dr. Davis what the chronological relationship is between the abnormal potentials of the brain and the appearance of the seizure. I have looked at the records published by Drs. Gibbs, Davis and Lennox (The Electro-Encephalogram in Epilepsy and in Conditions of Impaired Consciousness, ARCH. NEUROL. & PSYCHIAT. **34**:1133 [Dec.] 1935). It seemed to me, in some of the records at least, that the subject stopped making rhythmic movements of the hand before the abnormal wave appeared. I should like to know the sequence, because we are finding in some stutterers that the large waves which look similar to those shown in the slides occur invariably after the stuttering spasm is detected. That is, one can hear or see the spasm before the waves appear. They always cease, however, before the spasm is broken.

The other question is: What do these large, abnormally slow waves mean? If the subject is asked to respond to light, immediately following or simultaneously with the response there appears, in from 50 to 70 per cent of the records, large, slow waves, 3 or 4 per second, about half again as large as the regular wave appearing before the light flashed on and the response occurred.

Certainly, one would not say that the subject was having a seizure in making a very slight response, but in a high percentage of the records, simultaneously with or immediately following the occurrence of the action currents in the executant muscle, there occur 3, 4 or 5 of these large, slow waves, and they look similar to those that Dr. Gibbs showed as coming from the occipital lobe.

DR. GEORGE H. BISHOP, St. Louis: My remarks concern the comparison of the results of experiments on animals with the findings in human subjects just reported. In the optic cortex of the rabbit an "alpha" rhythm occurs of about one-half the frequency of the rhythm in man, or of from 3 to 7 waves per second, and a "beta" rhythm of twice the rhythm in man, or of from 30 to 80 waves, but with a similar variation of periodicity and amplitude. When strychnine and morphine, both of which are exciting drugs, are applied to the cortex, potential phenomena result comparable to those in cases of severe stuttering, petit mal and similar conditions, suggesting that waves of this form are not specific for a given cause but may result from any spastic state of the cortex.

In the optic cortex of the rabbit my associates and I have attempted to analyze the relation between the spontaneous response and the response to stimulation of the optic nerve. If a particular rabbit shows a marked spontaneous rhythm a single

electric shock applied to the optic nerve may cause a response if it falls during the surface-positive phase of the rhythm, but no response during the surface-negative phase. The response to stimulation, then, consists of a series of waves superposed on the spontaneous waves. If the spontaneous rhythm is less marked a shock in any phase of the cycle will cause a response, but a second shock is ineffective during the surface-negative phases of the response to the first. This response to a single stimulus is a repetitive series of waves of the same frequency as the spontaneous rhythm. The results indicate that the spontaneous rhythm signalizes a spontaneous fluctuation of excitability to optic nerve impulses, that a high amplitude of spontaneous waves results from synchronization of many elements and that the single shock is able to synchronize such elements even when they are initially asynchronous. In contrast to the single volley of impulses started by a shock, stimulation of the retina by light results in a random scattering discharge which tends to asynchronize such elements and thus causes the spontaneous rhythm to disappear from the record, although it presumably continues in each cortical element, these elements being out of phase with one another.

The spontaneous rhythm appears to involve more than the cortex; if the optic radiation is cut across just above the thalamus the alpha rhythm disappears with the abolition of the response to stimulation. The impulses of the spontaneous responses must therefore traverse a circuit from the thalamus to the cortex and back to the thalamus. At the surface-positive phase of the rhythm, during which the cortex is discharging to the thalamus, optic nerve impulses are effective; that is, the cortical impulses facilitate the passage of impulses from the optic nerve to the cortex. The time occupied by the spontaneous activity in traversing this circuit is one-fifth second, most of which is occupied in passage through the cortex itself, as is indicated by the cortical response to single stimuli. Since the spontaneous potentials obviously do not involve vision, the pathways occupied by the spontaneous facilitation circuits must be auxiliary to the visual pathways. Persistent stimulation of the retina by light causes a response from the cortex at its initiation, but not during its course, although cortical elements must still be responding, out of phase with one another. A single stimulus of the optic nerve causes a response of higher amplitude because the elements responding are synchronized. The greater stimulation occasions a lesser record of the response, which suggests that the cortical record may be an unsatisfactory measure of cortical activity.

DR. ERNEST A. SPIEGEL, Philadelphia: My associates and I have tried in the last year to study the meaning of the electro-encephalogram by comparing the cortical potentials with the potentials of various areas of the subcortex, particularly the optic thalamus and the cerebellum.

Adrian stated that the occipital lobe has something to do with the genesis of the slow waves. However, we discovered in our experiments on animals that if one extirpates the occipital lobe on both sides in cats these waves persist. One can still find these waves if one isolates the frontal cortex as far as possible, if one does not interfere with the blood supply.

On the other hand, when we studied the action potentials of the optic thalamus with needle electrodes after destroying the surface of the cortex, so that corticifugal impulses were abolished, we still noted waves from the optic thalamus that resembled the cortical potentials. These potentials of the optic thalamus responded in a similar way to various measures, for instance, to drugs that produced sleep. Increasing the distance of the electrode increases the waves in a similar way, as was noted in the case of the cortex. So one finds in this subcortical ganglion phenomena rather similar to those noted for the cortex.

As to the interpretation of the slow waves, I do not think that they are due to a simultaneous beat of small waves, because the simultaneous beat of small waves would never produce slow waves. These must be the result of a successive beat of the cells, due to a regular successive stimulation of cells in chains of neurons. Berger believed that these waves, which he called alpha waves, might indicate psychophysical phenomena. If one considers that we found these waves not only in the optic thalamus but also in the deeper part of the brain, such as the cerebellum, one must doubt whether one can go so far as to connect the alpha waves with psychophysical activity. All that can be said at present about these waves is that they show a fundamental type of activity of the gray matter that one finds in various parts of the cortex as well as the subcortex, and this indicates summation phenomena in chains of neurons.

Dr. Temple Fay, Philadelphia: I wish to make a few remarks regarding the paper of Dr. F. A. Gibbs, Dr. Lennox and Dr. E. L. Gibbs. Irrespective of the origin of the disturbance or of the electrical potential factors involved in the electroencephalogram, these authors have obtained a characteristic record of a subthreshold state which is associated with a phenomenon that neurologists choose to term the convulsion state or epilepsy (petit mal and grand mal). This method will probably make possible a diagnosis long before the outward symptoms of a convulsion arise.

The medical profession is going to be overburdened with a new group of patients, the subepileptic type. There appears to be no common agreement today as to the treatment for even the major state of the symptom complex. Now physicians have foisted on them a new group of patients, who will be considered as potential subjects for epilepsy. Whether or not they ever become so the electro-encephalogram cannot demonstrate. Physicians will be confronted with the question of what to do with the large group that they now have on their hands and with the potential group of the future.

Dr. Lennox was instrumental in organizing an American chapter of the International League Against Epilepsy last Tuesday night (May 5, 1936). Those interested in this problem will probably carry forward with two ideas: to standardize, from all the methods now being used, the most valuable recommendations of the medical profession for the treatment of the so-called convulsive disorders, based on pharmaceutic and other measures found beneficial by careful observations, and to analyze this problem further from the experimental standpoint.

The subthreshold or petit mal type of epilepsy is responsible for a great number of the present day accidents on the highways. Two years ago an automobile driven by a so-called normal person passed me so closely that I thought that the man had attempted to strike me. Observing him as he passed, I noted that the eyes were rolled up and the head was turned slightly. He returned to a normal position in time to prevent the machine from crashing into a tree.

A major task that physicians must carry out as a professional group is to combat the present propaganda which the ordinary commercial groups are putting out in pamphlet form and with good, scientific selection of statements made by the investigators particularly interested in this field. These firms are unjustly selecting a few statements to fortify their so-called method of treatment and advertise the product which they place on the market. Until physicians become interested in this problem from a unified standpoint, they will see patients with epilepsy improperly treated or eventually taken out of professional care.

I wish to reenforce Dr. Lennox' observation that attacks arise during a period of inactivity. Patients rarely have convulsions while swimming, running or going through active phases. During relaxation, however, the convulsive seizures are

frequent. Hence, my associates and I have utilized this factor in our program of treatment. We have obtained our best results from dehydration and dietary control and have subjected these patients to hard physical and mental work, gradually discontinuing the use of phenobarbital. Omission of the drug in itself is an important therapeutic factor. In my opinion, with the use of phenobarbital the fundamental process concerned with epilepsy goes on. That is the most important phase, rather than the convulsion itself. Phenobarbital brings only a false sense of security.

I wish to ask Dr. Lennox what influence the peripheral sensorium plays in bringing into activity the cortical potentials. In other words, if one removed the effect of the peripheral sensorium on the thalamic level, what influence would that have on the projection of the cortical spikes?

DR. HALLOWELL DAVIS, Boston: In regard to the bimodal distribution of frequencies and the significance of distinguishing between alpha and beta waves, we are convinced that there is a significant difference between the two. There is one group of frequencies in the neighborhood of 10 waves per second, which is seen often. We have repeatedly counted as many as one hundred samples in a record to see whether there is an equal distribution or a clumping on certain frequencies. There is such a group in the neighborhood of 10 waves a second. Frequencies of between 12 and 18 waves or thereabouts are relatively rare, but there is another group in the higher range. We have paid less attention to that higher range. It is smaller in voltage and harder to see.

I believe that the distribution of frequencies can be determined much more accurately with the help of a tuned amplifier. That is a technic which we are about to employ. I believe that the real answer in regard to this problem is still to be given.

We have checked our counts by having different observers make them independently. We agree well in the matter of identifying the frequencies and quite well in the estimates as to what percentage of time the alpha rhythm is clearly present, but this measurement also will be much more accurate with the tuned recording system.

In answer also to a question directed to Dr. Lennox: The physiologic experiment of eliminating the sensory impulses by cutting through the brain stem high up in the midbrain has been performed by Bremer, in Belgium. The cortex shows considerable activity, greatly resembling that during sleep or during anesthesia produced by one of the barbiturate series of drugs.

DR. GEORGE KREEZER, Vineland, N. J.: With regard to Dr. Travis' emphasis on the need for caution in the interpretation of results, I am in full agreement. The investigation which I have reported, for example, though it involved the use of a total of eighty-one subjects, can be regarded as indicating only trends, the particular directions in which more exhaustive studies should be made. I think that we now know the regions of the mental age scale in which it would be desirable to use a larger sampling of subjects in order to determine whether the differences indicated by the present study will turn out to be completely reliable statistically.

Dr. Travis inquired concerning the reliability of the differences that I reported as existing between different groups in the percentage of time occupied by regular rhythms in the total record. The figures reported were 52 per cent for a group of mentally normal adults and 48 per cent for a group of persons with the mongolian type of mental deficiency between mental ages of 6 and 7, on the one hand, and 21 per cent for a group of persons with the mongolian type of mental

deficiency between mental ages of 4 and 5 and 19 per cent for persons with the mongolian type of mental deficiency under a mental age of 4, on the other hand. The differences between the percentages for the first two groups are not statistically significant. However, there is evidence of a real difference between the percentage of either of the last two groups and that of the normal group. The critical ratios of the difference to the standard error of the difference are of the order of 2.5 or 2.7, which are on the borderline of statistical reliability.

Dr. Frederic A. Gibbs, Boston: Dr. Travis asked about the relationship between the time of the seizure as it appears clinically and the time of appearance of the large waves. That all depends on where the lead-off is being made. In the jacksonian seizure that I showed, if we had regarded the record from the right motor area we should have found that the seizure started before we saw any seizure waves. If we had regarded the record from the left motor area, we should have seen that the seizure waves began about ten or fifteen seconds before the seizure appeared clinically.

Our experience leads us to believe that the pathologic activity begins before the seizure appears. We have seen pathologic activity without the seizure, and it is only when the voltages become large and the activity is continued over a period of seconds that the clinical seizure develops.

As to Dr. Travis' interesting observations on stutterers, I do not know how much the waves in such cases look like ours. They seem to have a lower voltage. The question arises as to whether in leading these waves off the cortex he is getting them at their origin, in view of the fact that they come on so late in the attack of stuttering. If one leads off the occipital lobe, probably in 50 per cent of the petit mal seizures the wave will appear after the seizure has developed. As to Dr. Travis' observations on the large potential fluctuations which appear when a person responds to a command, I have no pertinent information. I wish to point out, however, that they seem to be much smaller than those that one sees in petit mal seizures. The smallest waves seen in petit mal seizures are about 100 microvolts and the largest over a millivolt.

Dr. William G. Lennox, Boston: Dr. Gibbs and Mrs. Gibbs and I have been dealing with a select group of patients, forty-nine of several thousand who have passed under our scrutiny for purposes of making records. They are patients who have frequent petit mal seizures, and they are not representative of the average patient who comes into the physician's office. We do not yet know the value of this technic in demonstrating subthreshold seizures in a patient who has only an occasional attack of grand mal.

We are fortunate in having in the exhibit a patient who illustrates the use of the electro-encephalogram, a patient furnished us by Dr. George Wilse Robinson of Kansas City. When I questioned her I was in doubt as to whether she was having attacks of petit mal or not. She complained of a slight feeling of jerking in her arm several times a day without disturbance of consciousness, but on the record we found that she was having frequently—every few minutes—disturbance of the electrical activity of the brain, lasting ten or fifteen seconds. During these periods the patient may or may not have the sensation of jerking. The only objective evidence is regularity in the blinking of the eyes. This technic should be of great value in diagnosis in certain special cases but perhaps not in the general run of cases.

VASOMOTOR TONUS OF THE DENERVATED ARTERY

CONTROL OF SYMPATHECTOMIZED BLOOD VESSELS BY SYMPATHOMIMETIC HORMONES AND ITS RELATION TO THE SURGICAL TREATMENT OF PATIENTS WITH RAYNAUD'S DISEASE

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THE PROBLEM OF RELEASING VASOCONSTRICTOR TONE BY SYMPATHECTOMY

Since the first attempts to relieve vasospasm in Raynaud's disease by sympathetic ramisection the results of the operation have been so variable that numerous modifications have been proposed in the technic of arterial denervation. Ganglionectomy has been found much more effective than ramisectomy because it is easier to make certain of resecting the nodal ganglia than to be sure of cutting all their delicate rami communicantes; also, because regeneration of the vasoconstrictor fibers is far less likely after this more radical but harmless procedure. Resection of the second and third lumbar ganglia is now established as a certain method for restoring an adequate circulation in favorable early cases of Raynaud's disease of the lower extremity. Twelve patients so treated at the Massachusetts General Hospital, after satisfactory response to procaine block, have all maintained an excellent circulation in the feet, with freedom from the previous color and trophic changes (the observations have extended over five years).

Sympathetic denervation of the arm by stellate ganglionectomy, however, has been far less satisfactory. At first the cervical approach failed because all the sympathetic connections with the brachial plexus were not divided. This defect was explained by Kuntz,[1] who showed that the second thoracic ganglion frequently sends a communicating ramus to the lowest trunk of the brachial plexus. With Kuntz' work

From the Surgical Laboratories of the Harvard Medical School at the Massachusetts General Hospital.

1. Kuntz, A.: Distribution of the Sympathetic Rami to the Brachial Plexus: Its Relation to Sympathectomy Affecting the Upper Extremity, Arch. Surg. **15**: 871 (Dec.) 1927.

in mind, Adson and Brown [2] developed a satisfactory method for resecting the inferior cervical and the first and second thoracic ganglia, all of which send gray rami to the brachial plexus. Provided these three structures are removed in toto, the arm is and remains completely sympathectomized. The sweat glands are permanently paralyzed, and the paralysis of the pilomotor muscles, even on local faradic stimulation, demonstrates that the entire network of postganglionic fibers has degenerated. In spite of complete denervation of the arm by the cervicothoracic operation, the results have been so unsatisfactory that Lewis [3] has been led to question the relation of excessive vasomotor activity to the cause of Raynaud's disease. He postulated that vasomotor tone in this condition is not increased, but that even in the early stages the spasm is due to a local fault in the smooth muscle of the digital arterioles. Lewis drew his conclusions from observations on the upper extremity. His interpretation does not seem satisfactory to us because it does not take into consideration the favorable results of lumbar ganglionectomy on the vessels of the lower extremity and neglects the abnormal activity of the sweat glands and the emotional factors which are so commonly associated with this disease.[4]

The discrepancy between the results of sympathetic ganglionectomy in the upper and the lower extremities of patients with Raynaud's disease has been baffling until recently. Among ten cases of the disease in the upper extremity which have been reviewed by one of us (White [5]) there were six in which partial improvement and four in which failure followed complete cervicothoracic ganglionectomy. In stating that six patients show partial improvement we mean that they have remained free from recurrent ulceration and have maintained a moderate increase in circulation. The hands are usually a little cooler than those of a

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2. Adson, A. W., and Brown, G. E.: The Treatment of Raynaud's Disease by Resection of the Upper Thoracic and Lumbar Sympathetic Ganglia and Trunks, Surg., Gynec. & Obst. **48**:577, 1929.

3. Lewis, T.: Experiments Relating to the Peripheral Mechanism Involved in Spasmodic Arrest of the Circulation in the Fingers; A Variety of Raynaud's Disease, Heart **15**:7, 1929.

4. Lewis deserves great credit for pointing out the early onset of obliterative changes in the digital arteries, which are present in all advanced cases of Raynaud's disease. In an article with Pickering, Lewis has recently somewhat modified his statement that arteriolar spasm in early cases of Raynaud's disease is due wholly to local pathologic change. (Lewis, T., and Pickering, G. W.: Observations upon Maladies in Which the Blood Supply to Digits Ceases Intermittently or Permanently, and upon Bilateral Gangrene of Digits; Observations Relevant to So-Called "Raynaud's Disease," Clin. Sc. **1**:327, 1934. Also, personal communication from Sir Thomas Lewis.) There is, consequently, no longer such a wide divergence between his views and those of the majority of workers in this country.

5. White, J. C.: The Autonomic Nervous System, New York, The Macmillan Company, 1935.

normal person on examination in relatively warm surroundings and during freedom from emotional stress. Either the latter factor or cold, however, may bring on a state of vasospasm. Such a limited degree of improvement was classified as successful by Ross[6] in his recent interesting review of the results of sympathectomy in England. In full agreement with us, Ross observed that for the first few weeks patients with this treatment uniformly show excellent circulation of the blood, but that some time later they wish that their hands had remained as warm as they were in the early postoperative period. In the series previously referred to, we are certain that the cervicothoracic portion of the sympathetic chain was completely removed, for the ganglia in each case were mounted on a card and preserved (fig. 1).

In the follow-up clinic these patients have been frequently tested, and the complete sudomotor and pilomotor paralysis has been maintained. Yet, after an initial period of a few weeks in which there was

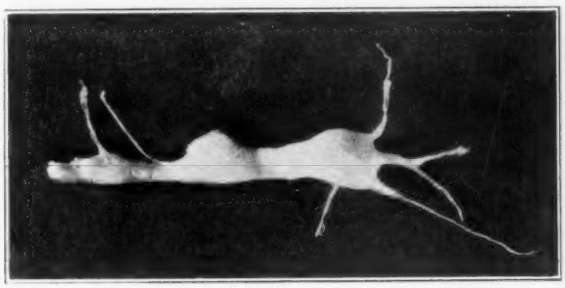

Fig. 1.—The inferior cervical and the first and second thoracic ganglia as they appear after complete cervicothoracic ganglionectomy. (From White, J. C.: Raynaud's Disease: Studies on Post-Operative Cases Bearing on the Etiology of the Disease and the Efficiency of Sympathetic Ganglionectomy, *New England J. Med.* **206**:1198, 1932.)

a striking increase in circulation, the temperature of the fingers on exposure in a cool room (70 F.) may now reach the low level of from 78 to 73 F.[7] The stimuli of both cold and emotion have often been observed to produce recurrent cyanosis of the hands, although in patients in whom lumbar ganglionectomy has also been performed the feet remain hot (from 92 to 85 F.) and normal in color. We have

6. Ross, J. P.: The Results of Sympathectomy: An Analysis of the Cases Reported by Fellows of the Association of Surgeons, Brit. J. Surg. **23**:433, 1935.

7. Before operation the surface temperature often fell as low as from 68 to 66 F. in a room at 70 F. This cooling below the temperature of the room, which is due to abnormal sweating and evaporation, is eliminated by sympathectomy and the resultant sudomotor paralysis.

seen the hands of an unusually nervous woman with Raynaud's disease become cyanotic on presentation for demonstration before a group of medical students within a fortnight after a meticulous cervicothoracic operation. This dramatic observation brought all enthusiasm for this operation to an end and led to an interchange of views with other surgeons who have been interested in the problems of chronic vascular disease. The great majority of the answers to our questionnaire revealed that results at other clinics were similar to our own; uniform success after lumbar ganglionectomy, but inadequate improvement after the cervicothoracic operation. This appears to be the case regardless of whether the operation has been performed through the posterior approach or through Gask's [8] modification of the cervical incision with transection of the scalenus anticus muscle. Adson's [9] reports have constituted the outstanding exception to this nearly universal feeling of dissatisfaction, although even he admitted that his results in the arms were not so satisfactory as those in the lower extremities.

We were at this stage of uncertainty three years ago when a clue to the possible cause of the residual ability of denervated arteries to constrict was given us by Dr. Norman E. Freeman, who had recently been transferred from the department of physiology. This involved the principle, well known to physiologists since the work of Elliott,[10] that denervated smooth muscle becomes abnormally sensitive to epinephrine reaching it in the blood stream. The Meltzers [11] had first called attention to this phenomenon in the denervated ear of a rabbit. Meltzer and Auer [12] then made the observation that a dose of epinephrine too small to affect the normal iris caused a wide pupillary dilatation on the side from which the superior cervical sympathetic ganglion had been removed, provided sufficient time for axonal degeneration had elapsed. Hartman, McCordock and Loder [13] later observed that the denervated iris which has dilated during ether anesthesia and operative trauma reassumes the fully contracted position as soon as both adrenal glands

8. Gask, G. E.: The Surgery of the Sympathetic Nervous System, Brit J. Surg. **21**:113, 1933.

9. Adson, A. W.: Indications for Operation on the Sympathetic Nervous System, J. A. M. A. **106**:360 (Feb. 1) 1936.

10. Elliott, T. R.: The Action of Adrenaline, J. Physiol. **32**:401, 1905.

11. Meltzer, S. J., and Meltzer, C.: The Share of the Central Vasomotor Innervation in the Vasoconstriction Caused by Intravenous Injection of Suprarenal Extract, Am. J. Physiol. **9**:147, 1903.

12. Meltzer, S. J., and Auer, C. M.: Studies on the "Paradoxical" Pupil-Dilatation Caused by Adrenalin: I. The Effect of Subcutaneous Injections and Instillations of Adrenalin upon the Pupils of Rabbits, Am. J. Physiol. **11**:28, 1904.

13. Hartman, F. A.; McCordock, H. A., and Loder, M. M.: Conditions Determining Adrenal Secretion, Am. J. Physiol. **64**:1, 1923.

have been removed. Cannon, Lewis and Britton [14] attempted to prevent cardiac acceleration by denervation and found this to be impossible until the adrenal glands had been inactivated. The completely denervated heart is sensitive to 1 part of epinephrine in 1,400,000,000.

Freeman, Smithwick and White [15] applied these principles to arterial smooth muscle. They found that the rabbit's ear after superior cervical ganglionectomy cools almost to room temperature during the secretion of epinephrine that occurs in the course of hypoglycemia caused by insulin. This intense vasoconstriction, which develops within a week after ganglionectomy, is eliminated after resection of one adrenal gland and denervation of the other (fig. 2). Smithwick, Freeman and White [16] demonstrated that in the human being in whom cervicothoracic ganglionectomy has been performed a striking response occurs both on intravenous injection of very dilute quantities of epinephrine (fig. 3) and on stimulation of the adrenal glands by insulin-induced hypoglycemia (fig. 4). Figure 3 also makes it apparent that sympathectomized fingers are far more sensitive than sympathectomized toes. As a result of these observations we became impressed with the importance of sympathomimetic hormones in the regulation of the tone of denervated arteries. The next step was to find out why this factor should play so much more important a rôle in the upper than in the lower extremity.

EXPERIMENTAL OBJECTIVE

To shed further light on the problem of residual arterial spasm in human hands after cervicothoracic ganglionectomy, a series of experiments was carried out on thirty-five albino rabbits and three monkeys (Macacus rhesus).

EXPERIMENTS ON RABBITS

1. *Acute Denervation by Infiltration with Procaine.*—The simplest method of producing acute denervation of the rabbit's ear is to infiltrate the tissue at its base with a 1 per cent procaine solution. When this is done the vessels in the ear become widely dilated. The reaction

14. Cannon, W. B.; Lewis, J. T., and Britton, S. W.: Studies on the Conditions of Activity in Endocrine Glands: XVII. A Lasting Preparation of the Denervated Heart for Detecting Internal Secretion, with Evidence for Accessory Accelerator Fibers from the Thoracic Sympathetic Chain, Am. J. Physiol. **77**:326, 1926.

15. Freeman, N. E.; Smithwick, R. H., and White, J. C.: Adrenal Secretion in Man: The Reactions of the Blood Vessels of the Human Extremity, Sensitized by Sympathectomy, to Adrenaline and to Adrenal Secretion Resulting from Insulin Hypogycemia, Am. J. Physiol. **107**:529, 1934.

16. Smithwick, R. H.; Freeman, N. E., and White, J. C.: Effect of Epinephrine on the Sympathectomized Human Extremity: An Additional Cause of Failure of Operations for Raynaud's Disease, Arch. Surg. **29**:759 (Nov.) 1934.

involves the entire arterial tree and the minute vessels as well, as evidenced by the reddened ground tone of the ear. Thermal and psychic stimuli cause no perceptible constrictor response. This procedure corresponds to the procaine tests commonly used in human beings. That the results may be misleading becomes apparent when they are compared with the late results of chronic denervation.

2. *Complete Denervation with Degeneration of Postganglionic Neurons.*—According to Feldberg,[17] excision of the superior cervical sym-

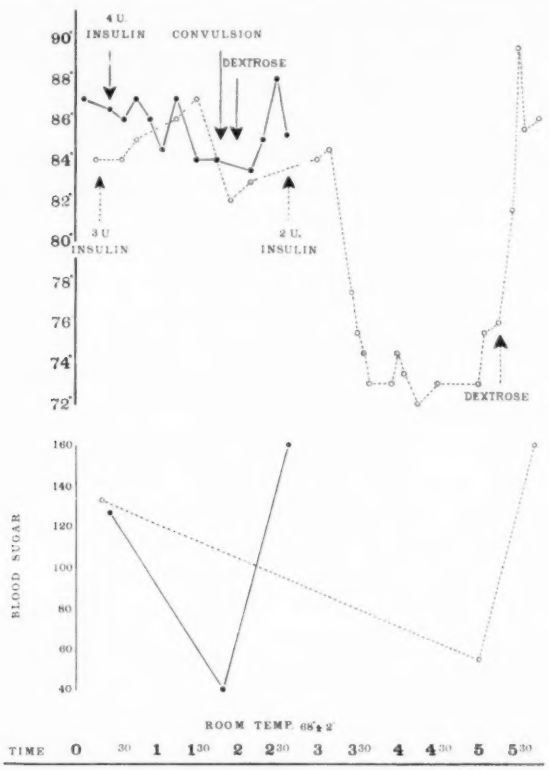

Fig. 2.—The surface temperatures of the denervated right ear and the blood sugar levels of a rabbit during insulin-induced hypoglycemia before (broken lines) and after (solid lines) removal of the left and denervation of the right adrenal gland. The arrows indicate the points of time at which insulin and dextrose were injected intraperitoneally and a convulsion was experienced by the rabbit after the adrenal operation. (From Freeman, Smithwick and White; [15] reproduced with the permission of the *American Journal of Physiology.*)

17. Feldberg, W.: The Peripheral Innervation of the Vessels of the External Ear of the Rabbit, J. Physiol. **61**:518, 1926.

pathetic ganglion plus the great and posterior auricular nerves should produce complete denervation of the ear. Grant, Bland and Camp,[18] however, have shown that in addition it is necessary to cut the auricular branch of the vagus nerve (Arnold's nerve) and the auriculotemporal branch of the trigeminal nerve. In our first experiments all of these were cut, but in the later ones the last nerve was left intact, as it is rather difficult to find and supplies only a small lateral area at the base of the ear, well below the point under observation. The other nerves, however, are important in any attempt to destroy all the postganglionic sympathetic neurons. While these reach the auricular vessels mainly through the superior cervical ganglion, an appreciable number run from the stellate ganglion over its vertebral ramus to the great and posterior auricular nerves, possibly to Arnold's branch of the vagus nerve as well.

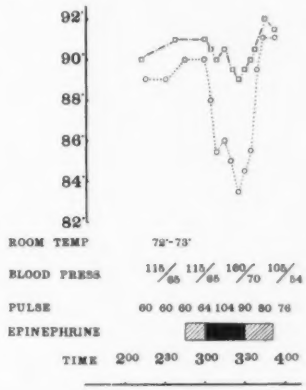

Fig. 3.—Effect of an injection of a solution of epinephrine in a patient (P. R.) after sympathetic denervation of the four extremities. The dot-dash line represents the response, as shown in the temperature of the left first toe, sixteen months after operation; the dotted line, the response, as shown in the temperature of the left thumb, six months after operation. The chart shows that after cervicothoracic ganglionectomy the hands were markedly sensitized to epinephrine and that the feet were very slightly sensitized. (From White;[5] reproduced with the permission of The Macmillan Company, New York.)

After these nerves have been severed, the distal two thirds of the ear becomes insensitive and the entire terminal network of nerve fibers degenerates. During the first day the auricular vessels remain widely dilated, and the ground tone of the ear is distinctly reddened (fig. 5 *A*). The full intensity of this reaction is, however, short-lived. On the second day the ground tone is distinctly less red; according to Grant, Bland and Camp,[18] this fading out in capillary dilatation can be detected

18. Grant, R. T.; Bland, E. F., and Camp, P. D.: Observations on the Vessels and Nerves of the Rabbit's Ear with Special Reference to the Reaction to Cold, Heart **16**:69, 1932.

within two hours. From this time on the animal shows a progressive return of vasomotor tone. Figure 5 *B* shows the state of the vascular tree in the right ear eight days after denervation. In this animal, as well as in nineteen others, it was observed that when the rabbit was asleep or at rest in a warm, quiet place the deneverated vessels remained moderately dilated (diameter of the main artery at the center of the ear, from 0.6 to 0.8 mm.[19]). At this time the fully dilated central artery

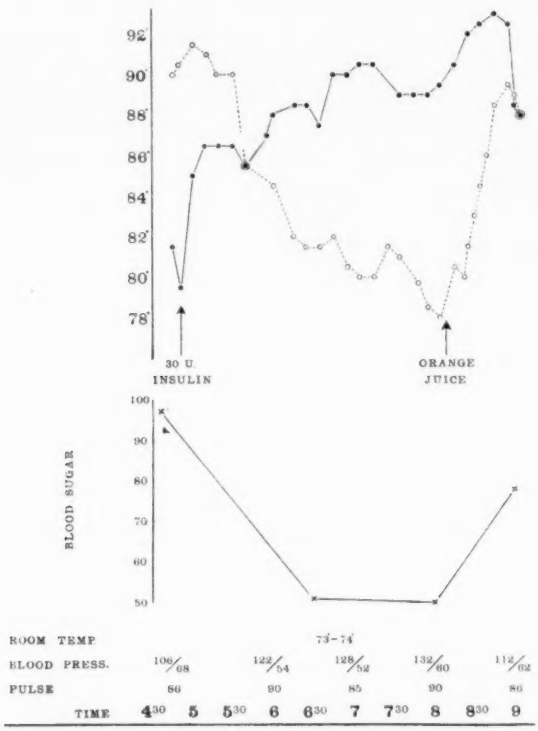

Fig. 4.—Vasomotor responses in the hands of a patient (R. F.) on insulin excitation of the adrenal medulla. Vasoconstriction (broken line) is shown in the left fifth finger after nerve degeneration, and vasodilatation (solid line) in the corresponding normal extremity. (From Freeman, Smithwick, and White;[15] reproduced with the permission of *The American Journal of Physiology*.)

of the control ear was distinctly larger (from 1 to 1.2 mm.). When, however, such an animal was exposed to cold, fear or painful stimuli,

19. In our rabbits measurements of the external diameter of the main auricular artery at the middle of the ear gave uniform average readings, viz.: maximal constriction, 0.2 mm.; maximal dilatation, from 1.2 to 1.5 mm. in the larger animals; average with animal at rest comfortably warm, from 0.8 to 0.6 mm.

or merely when it began to exercise, the denervated central artery constricted as completely as the normal control. Closer scrutiny revealed that on the commencement of exertion the denervated artery constricted a few seconds after the artery in the control ear, with its nerves intact. This reaction developed with such regularity that it became impossible to photograph any of these chronically denervated ears in the state of

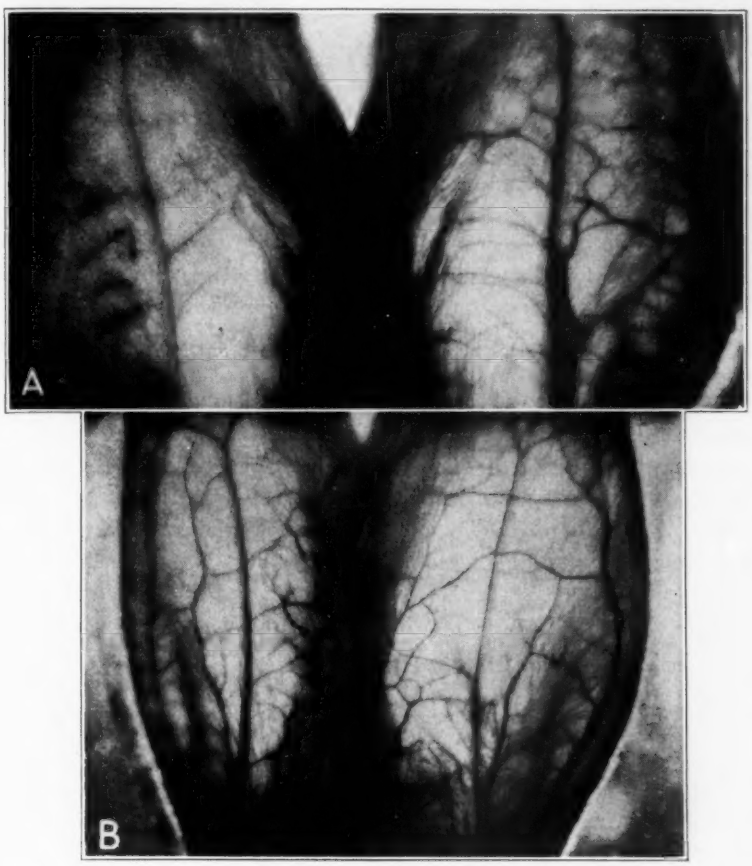

Fig. 5.—*A*, maximum vasodilatation in the denervated right ear of a rabbit twenty-four hours after section of the postganglionic sympathetic neurons. The temperature of the room was 56 F. *B*, maximum vasocontriction in the denervated right ear of a rabbit eight days after destruction of the postganglionic sympathetic neurons. The temperature of the room was 72 F. (From White;[5] reproduced with the permission of The Macmillan Company, New York.)

vasodilatation. The psychic stimulation of restraining the rabbit in an animal box and transilluminating its ears was sufficient to throw the denervated artery into maximal constriction. This state seemed to last

a long period, although the arteries in the normal ear soon relaxed in a room the temperature of which was over 70 F.

It is interesting in this connection to quote from Grant, Bland and Camp,[20] who wrote:

> It seems to us possible that the smaller calibre of the denervated vessels during bodily activity and after fright may be due to the release of adrenaline which is believed to occur under these conditions, and that the loss of tone when the animal is at rest or under luminal is due to a decrease in the amount of circulating adrenaline.

At the time of this report they had not proved this interesting theory.

3. *Effect of Adrenal Inactivation on Vascular Tone of Denervated Ear.*—Evidence was obtained by Freeman, Smithwick and White [15] that resection of one adrenal gland and denervation of the other would eliminate the fall in the temperature of the skin of the denervated ear which had been observed during insulin-induced hypoglycemia (fig. 2). To test this matter further the adrenal glands were inactivated in three rabbits which had shown marked vasospasm in the denervated vessels on exertion, cold or emotional stimuli. The left adrenal gland was resected, and the right was denervated by cutting the splanchnic nerves below the diaphragm in addition to removing the upper portion of the lumbar sympathetic chain. In these animals the residual ability of the denervated arteries to constrict was largely abolished (fig. 6). The state of arterial relaxation, although constant, was not complete. Struggle resulted in a barely detectable narrowing of the denervated arteries, but prolonged exposure to cold produced definite constriction (see protocol of rabbit 13).

Rabbit 2: The animal was a female, weighing 2.26 Kg. On Feb. 7, 1934, sensory denervation of the right ear was obtained by resection of the great and posterior auricular nerves as well as of Arnold's nerve. Following this operation the distal two thirds of the ear became anesthetic, but there was no visible change in the ability of the arteries to constrict.

On February 14, resection of the right superior cervical sympathetic ganglion was performed. There ensued striking vasodilation in the ear on the sympathectomized side, which involved all the vessels down to the capillary network. Within three days, however, the reddened ground tone had blanched out, and on the fifth day it was observed that in a room at 70 F. after a struggle the denervated vessels remained smaller than those of the normal ear. Three weeks after operation struggling caused vasoconstriction in the denervated ear, which persisted as long as the animal was observed.

On March 9, inactivation of the adrenal glands was effected Following the elimination of the secretion of these glands this animal was observed frequently. Struggle and fright now caused barely detectable constriction of the denervated arteries (fig. 6). Ten days after operation snuffles developed, and the animal rapidly became moribund. Even at this stage, with a rectal temperature reduced

20. Grant and others,[18] p. 91.

to 90 F., the arterial tree in the right ear remained moderately dilated (0.5 mm.) while that in the left was intensely constricted (0.2 mm.).

Rabbit 13: The animal was a female of moderate size. On March 21, 1934, the nerves at the base of one ear were cut, and the superior cervical sympathetic ganglion was resected at one stage. Eight days later the denervated arteries showed maximum sensitivity to circulating vasoconstrictor hormones. On April 16, resection of the left adrenal gland and denervation of the right were carried out. The arterial tree became fully dilated and lost its ability to constrict on painful stimulation. When the rabbit was observed on two occasions (May 1 and 10)

Fig. 6.—Persistent vasodilatation of the right ear of a rabbit after section of postganglionic sympathetic neurons and subsequent inactivation of the adrenal glands. The temperature of the room was 70 F. (From White;[5] reproduced with permission of The Macmillan Company, New York.)

TABLE 1.—*Observations on Rabbit 13*

Time	Surface Temperature and Diameter of Central Artery: Right (Denervated) Ear		Left (Control) Ear		Rectal Temperature	Room Temperature	Comment
11:10	90 F.	0.7 mm. (fixed)	88 F.	1 to 0.3 mm. (variable)	103.2 F.	74 F.	
11:50	.....	.....	.....	.....	.....	.....	Rabbit received 100 cc. of ice water
12:05	85 F.	.....	82 F.	.....	103 F.	.....	Vessels of right ear much larger, although blood flow is very slow
12:20	.....	0.5 mm.	.....	0.25 mm.	.....	.....	
12:30	88 F.	.....	85.5 F.	.....	102.4 F.	.....	
12:38	89 F.	.....	89 F.	.....	.....	.....	Vessels of both ears are dilated, but left constricts on struggle

struggle resulted in a slight further dilation of the denervated arteries, secondary to the rise in systemic blood pressure, while the arteries in the control ear showed complete constriction. On April 24, 100 cc. of ice water was administered by stomach tube to cause a reduction in body temperature. The vasomotor reaction in the denervated and control ears are shown in table 1.

In another animal with adrenal glands intact, which was tested in a similar manner, the denervated ear cooled and exhibited a vasoconstrictor response as great as that of the normal ear.

Rabbit 13 was observed for two months. At the end of this period it was obvious that the denervated remaining adrenal gland was regaining its ability to secrete. Autopsy showed no residual adrenal tissue on the left, but the gland on the right was hypertrophied. Although regenerated lumbar and splanchnic rami could not be traced to this gland, there can be little doubt but that fine connections had led to further secretory activity. This is analogous to the observations of Cannon, Lewis and Britton [14] on the regeneration of these nerves when they used the denervated heart as an indicator.

4. *Effect of Degeneration Limited to Preganglionic Neurons.*—The original experiments of Meltzer and Auer [12] demonstrated that postganglionic section was more effective than preganglionic in augmenting sensitivity to injected epinephrine. In order to compare the effect of destroying the preganglionic with that of destroying the postganglionic portion of the sympathetic motor pathway to the arteries of the rabbit's ear, it is necessary first to recall the anatomy of these fibers.

The preganglionic neurons, the cells of origin of which lie in the intermediolateral column in the lateral horn of the thoracic portion of the spinal cord, traverse the anterior spinal roots and white rami communicantes to the chain of paravertebral sympathetic ganglia. Langley [21] showed that the fibers destined for the ear emerge over the motor roots from the first to the fifth thoracic segment. On reaching the sympathetic chain they run upward over a large number of segments. Most of them run in continuity to the superior cervical ganglion, where they form synapses with the postganglionic neuron cells. In addition, a few postganglionic fibers originate in the stellate ganglion and run over its vertebral ramus to the great and posterior auricular nerves. Cutting the upper thoracic anterior spinal roots or resection of the stellate and upper thoracic ganglia is therefore an effective manner of insuring degeneration of the preganglionic portion of the vasoconstrictor pathway.

Laminectomy and division of the upper thoracic spinal roots was carried out in three rabbits (27, 28 and 29). This operation is not easy to perform in the rabbit because of difficulties with anesthesia and hemorrhage and because the cord fills up such a large portion of the bony canal. We found it necessary to sacrifice the posterior roots in order to obtain good exposure of the anterior. These animals recovered from the operation successfully, but showed slight to moderate paralysis in the lower extremities, which made it difficult to main-

21. Langley, J. N.: On the Origin from the Spinal Cord of the Cervical and Upper Thoracic Sympathetic Fibers, with Some Observations on White and Grey Rami Communicantes, Phil. Tr. Roy. Soc., London, s.B **183**:85, 1892.

tain a normal state of nutrition. One animal (*27*) remained in fair condition for two months, and it was possible to make valid observations on the circulation in all three. In each there was a minimal response to cold, excitement and injected epinephrine.

Rabbit *27*: The animal was a female, weighing 5.2 Kg. On May 14, 1934, section of the posterior and anterior spinal roots 2_2 to T_6 (right) was performed. A week later this animal was in good condition. There was only slight residual paralysis of the hindlimbs. Figure 7 shows that the vascular tree was in a state of dilatation even though the animal was uncomfortable and frightened. This should be contrasted with figure 5 *B*, which shows a high degree of vasospasm in an ear denervated by degeneration of the postganglionic neurons. On struggle or painful stimulation the degenerated right ear showed an ability of the arterial

Fig. 7.—Persistent vasodilatation of the right ear of a rabbit after destruction of the preganglionic sympathetic neurons on the right side by sectioning the upper five thoracic spinal roots. The temperature of the room was 70 F. (From White;[5] reproduced with the permission of The Macmillan Company, New York.)

tree to constrict slightly (1.1 to 0.8 mm.), while the vascular tree in the normal ear shut down completely (1.5 to 0.2 mm.). This minimal response may mean either: (1) that a few vasoconstrictor fibers remained intact, coming from the first thoracic or from below the sixth thoracic segment, or (2) that degeneration of the preganglionic neurons is followed by slight sensitization to epinephrine. Constriction of this slight degree appeared to be the greatest of which the denervated vessels were capable. Prolonged exposure to cold in the laboratory refrigerator produced the reactions shown in table 2 (June 1):

On June 20, the experiment described was repeated and gave nearly identical results.

On July 8, the vascular tree in the right ear remained dilated at 0.8 mm. When the animal was killed with chloroform, the denervated arteries did not constrict.

In contrast, vasoconstriction was a constant observation in other animals after degeneration of the postganglionic neurons if the adrenal glands had been left intact.

Rabbits 28 and 29: In these two rabbits the results following degeneration of the preganglionic neurons were practically identical. In rabbit 28, after we observed the very slight vasospasm that developed on stimulation of the sympathoadrenal system, we performed postganglionic denervation. As a result the vascular tree became extremely sensitive to circulating vasoconstrictor substances and within a week constricted to a maximal degree (0.2 mm.) after struggle, chilling of the body or injection of epinephrine.

An alternative method of interrupting the preganglionic fibers to the ear consists in resection of the inferior cervical and the first and second thoracic sympathetic ganglia. This operation was performed through an axillary incision with removal of the central portion of

TABLE 2.—*Observations on Rabbit 27*

	Surface Temperature and Diameter of Central Artery						
	Right (Decentralized*) Ear		Left (Control) Ear		Rectal Temperature	Room Temperature	
Time							Comment
9:50	.....	1.0 mm.	.....	1.0 to 0.2 mm.	.....	.....	
10:00	96 F.	1.0 mm.	96 F.	1.2 mm.	103 F.	77 F.	
10:15	.....	.....	.....	.....	.....	39 F.	Placed in refrigerator
12:15	86 F.	0.8 mm.	66 F.	0.2 mm.	99 F.	39 F.	
12:30	.....	.....	.....	.....	.....	77 F.	Replaced in warm room
4:05	88 F.	1.0 mm.	86 F.	1.2 mm.	101 F.	70 F.	

* Here and in later experiments we shall refer to the extremity on the side in which the preganglionic fibers had been cut as the decentralized ear or hand.

the second rib, after Dr. H. H. Bradshaw had devised a method of inserting an intratracheal catheter past the small, deep-set larynx of the rabbit. Two animals were carried through this operation successfully, and thereby we were enabled to study the effects of preganglionic denervation after a less mutilating operation. These rabbits remained in excellent condition and consistently showed changes similar to those just reported, viz., very slight vasoconstriction on exposure to cold, following emotion, during insulin hypoglycemia or after a direct injection of epinephrine.

As both animals showed identical responses, the protocol of only one will be given.

Rabbit 30: The animal was a female, white, weighing 5 Kg. On Nov. 15, 1934, left cervicothoracic ganglionectomy was done under intratracheal ether anesthesia without complications.

On November 19, the red ground tone which followed the acute decentralization was blanching out.

After November 21 and through the next eight weeks, at repeated examinations, the central artery in the decentralized left ear was always maintained at a diameter of from 0.9 to 0.7 mm. Neither struggle nor fright nor pain caused further vasoconstriction in this ear, whereas each produced maximal vasoconstriction (0.2 mm.) in the normal ear.

On Jan. 11, 1935, after the rabbit was left out of doors in the shade at 48 F. and the rectal temperature had fallen to 100.8 F., the observations on the ears were as shown in table 3.

TABLE 3.—*Observations on Rabbit 30*

Time	Surface Temperature and Diameter of Central Artery: Left (Decentralized) Ear		Right (Control) Ear		Pulse	Rectal Temperature	Room Temperature	Comment
Jan. 11, 1935	85 F.	0.7 mm.	70 F.	0.3 mm.	...	.....	.....	Vessels much more numerous and larger throughout
Feb. 6, 1935 11:35	89 F.	0.7 mm.	88 F.	0.5 mm.	...	103 F.	68 F.	Injected 1 cc. of 1:1,000 solution of epinephrine subcutaneously
12:00	87 F.	0.6 mm.	85 F.	0.3 mm.	156	.....	.....	
12:15	90 F.	0.7 mm.	80 F.	0.2 mm.	...	.....	.....	
12:45	89 F.	0.7 mm.	83 F.	0.2 mm.	200	.....	.....	
1:00	90 F.	0.7 mm.	88 F.	0.8 mm.	...	.....	68 F.	
1:30	90 F.	0.8 mm.	83 F.	0.2 mm.	208	.....	.....	
2:00	89.5 F.	0.8 mm.	87.5 F.	0.6 mm.	148	104 F.	72 F.	
Feb. 8, 1935 12:15	90 F.	0.6 mm.	84 F.	0.2 mm.	...	.....	72 F.	Blood sugar, 72 mg.
12:24	.....	.....	.....	.....	...	.....	.....	Insulin, 10 units, intramuscularly
1:45	87 F.	0.8 mm.	76 F.	0.2 mm.	...	.....	.....	
2:15	86 F.	0.8 mm.	87 F.	1.0 mm.	...	.....	.....	First signs reaction to insulin
2:30	87 F.	0.7 mm.	91 F.	1.2 mm.	...	.....	.....	Mild convulsion
2:50	86 F.	0.6 mm.	90 F.	1.2 mm.	...	.....	.....	More severe convulsion; blood sugar, 27 mg.
3:45	87 F.	0.5 mm.	90 F.	1.0 mm.	...	101 F.	71.5 F.	Continuous convulsions, unconsciousness and death

On February 6, a solution of epinephrine was injected, with results as shown in table 3. On the following day intravenous injection of 1 cc. of a 1 : 100,000 solution of epinephrine produced a response identical with that observed on the previous day but lasting only ten minutes. On February 8, stimulation of adrenal secretion by insulin induced hypoglycemia gave results as shown in table 3.

Contrast with this slight circulatory response in the ear denervated by preganglionic section the response in three animals after postganglionic denervation, when the blood sugar had fallen to convulsive levels (rabbit 32, 53 mg.; rabbit 33, 46 mg.; rabbit 34, 43 mg.). In these animals the temperature of the denervated ear fell 14.5, 13

and 15 degrees, corresponding to a maximal constriction of the central artery to 0.2 mm., while the normal ears showed the characteristic paradoxical vasodilatation.

EXPERIMENTS ON MONKEYS

The experiments which have just been reported demonstrate the ability of the smooth muscle in the arteries of the rabbit's ear to constrict after complete degeneration of the vasomotor nerves. This reaction is mediated by circulating chemical substances, the most important of which is the secretion of the adrenal medulla. Having found that this response is slight after destruction of the preganglionic portion of the vasoconstrictor pathway but very striking after the postganglionic neurons have degenerated, the next important step was to observe whether a similar relation existed in the monkey's hand. While on first thought the mechanism which controls the circulation in the rabbit's ear may appear unrelated to that in the human extremity, there exists an important fundamental physiologic relationship in that both are thermoregulatory organs and far more sensitive to changes in the tonic activity of the sympatho-adrenal system than other areas of the body (Grant, Bland and Camp;[18] Coller and Maddock[22]). It seemed advisable, however, to retest these differences in the behavior of the unstriated muscle of the rabbit's ear in an extremity more closely related to the human hand. The hand of the monkey (Macacus rhesus) was chosen for this purpose because it resembles the human hand in its vasomotor and sudomotor reactions and because this animal is well suited to intraspinal and intrathoracic operations and to subsequent laboratory tests.

Using intraperitoneal sodium amytal anesthesia, as recommended by Fulton and Keller,[23] two animals were prepared. In order to interrupt the entire preganglionic outflow to the brachial plexus, we followed the anatomic findings of Langley[21] and cut the anterior spinal roots from the fourth through the tenth thoracic segment. We had observed previously that section of a lesser number of roots failed to produce complete vasomotor paralysis. Postganglionic degeneration was accomplished by cervicothoracic ganglionectomy as recommended by Adson for the treatment of Raynaud's disease. In one animal (Sam) these two procedures were carried out on opposite sides and thereby afforded an excellent opportunity for comparing the resultant responses. In

22. Coller, F. A., and Maddock, W. G.: The Function of Peripheral Vasoconstriction, Ann. Surg. **100**:983, 1934.

23. Fulton, J. F., and Keller, A. D.: Observations on the Response of the Same Chimpanzee to Dial, Amytal and Nembutal, Used as Surgical Anaesthetics. Surg., Gynec. & Obst. **54**:764, 1932.

the second, only unilateral anterior rhizotomy was done, leaving the opposite arm for a control. As the reactions observed after the latter procedure were identical in the two animals, only those in the first will be described.

Monkey "Sam:" The animal weighed 3.76 Kg. On April 4, 1935, cervicothoracic ganglionectomy was performed on the left side. Under intraperitoneal administration of sodium amytal (0.6 cc. of a 10 per cent solution per kilogram of body weight) and intermittent intratracheal insufflation of air, the central portion of the second rib was resected through an axillary incision. The apical pleura was separated from the bodies of the three upper thoracic vertebrae. In this process a rent was made in the pleura, but as the lung was kept well expanded this complication had no adverse effect on the animal's condition. An excellent exposure was thus obtained of the sympathetic trunk, which was resected from above the inferior cervical to below the second thoracic ganglion. Recovery was rapid, and the monkey presented a well marked Horner's sign and a hot, dry hand.

On April 17, injection of 1 cc. of a 1:1,000 solution of epinephrine was followed by a fall in the surface temperature of the sympathectomized fingers from 86 to 74.5 F., without any change on the normal side (rectal temperature, 101.7 F.; room temperature, from 68 to 70 F.).

On May 17, this experiment was repeated, 0.5 cc. of epinephrine being used, with an identical response. Extreme hypersensitivity to circulating epinephrine was observed.

On May 24 and 31, the spinal roots from T_4 through T_{10} on the right side were cut intradurally in two stages. Horner's syndrome did not develop on this side, and the monkey showed remarkably little after-effects from these extensive operations. Five days after the second intervention, when he was strapped down, both hands were completely dry. After the irritation of an hour's restraint there was no change in the surface temperature of the right hand, but the fingers of the left hand (postganglionic denervation) had fallen from 86 to 81 F. This fall must be ascribed to the effect of chemical mediators secreted in response to emotional stimuli and reaching the responsive mechanism in the smooth muscle cells of the arteriolar walls via the blood stream. As in the rabbit's ear after postganglionic denervation, so in the left hand of the monkey we observed a striking vasoconstrictor response whenever the animal became irritated, frightened or cold.

Two weeks after the second operation, when time for complete degeneration of the preganglionic neurons had elapsed, the monkey was subjected to a final test with epinephrine. The fundamental differences in the responses of the two hands are recorded in table 4 and are plotted in figure 8.

This experiment constitutes a clearcut demonstration of the importance of performing sympathetic denervation on the preganglionic neuron of the vasoconstrictor pathway. On discussing the significance of these observations with other workers in this field, only one objection has been raised to our explanation of the different results following the two operations. It is that gray rami communicantes may run to the brachial plexus from that part of the sympathetic trunk which is below the second thoracic ganglion. Such connections would be interrupted by anterior rhizotomy carried as low as the tenth thoracic segment but might be missed by the standard cervicothoracic operation

TABLE 4.—*Observations on Monkey "Sam," June 14, 1935*

Time	Temperature of Palm at Base of Fingers: Right (Preganglionic Denervation)	Temperature of Palm at Base of Fingers: Left (Postganglionic Denervation)	Pulse	Rectal Temperature	Room Temperature	Comment
11:24	89.0 F.	87.5 F.	...	101.2 F.	73.5 F.	
11:25	.....	.....	...	.....	.....	0.25 cc. of 1:1,000 solution of epinephrine subcutaneously
11:32	87.5 F.	86.0 F.	...	.....	.....	
11:45	85.5 F.	82.0 F.	180	.....	74.0 F.	
12:01	86.0 F.	81.0 F.	256	.....	74.0 F.	
12:15	85.0 F.	80.0 F.	240	.....	74.0 F.	Shivering
12:30	87.0 F.	79.5 F.	240	97.5 F.	74.5 F.	

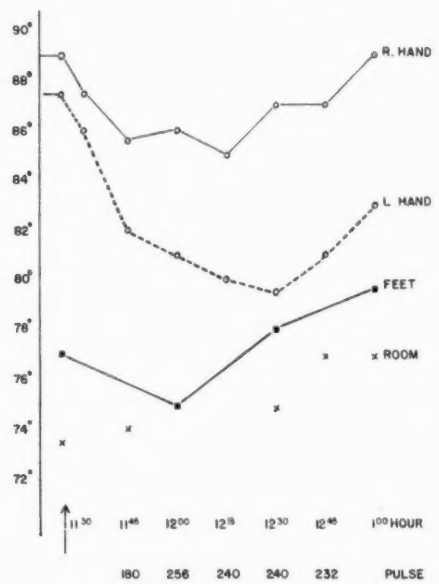

Fig. 8.—The vasoconstrictor effect of epinephrine on monkey "Sam's" hands after preganglionic and after postganglionic denervation. An arrow indicates the point of time at which 0.25 cc. of a 1:1,000 solution of the hormone was injected. The light solid line represents the response, in the temperature, in the right hand (spinal roots T_1 to T_{11} cut). The broken line represents the response in the left hand (cervicothoracic ganglionectomy). The heavy solid line represents the temperature of the feet as normal controls. Contrast the nearly maximal fall of the left hand after cervicothoracic ganglionectomy with the slight drop in the decentralized right hand. This hand showed no fall on excitement; the other showed exactly the same fall with excitement alone.

of Adson. In fact, this has been the common clinical explanation for poor operative results in early cases of Raynaud's disease even when sudomotor and pilomotor paralysis has remained complete. If this explanation is valid, a resection which includes the entire inferior cervical and the upper six or seven thoracic sympathetic ganglia ought to give results as good as those observed in "Sam's" right hand; but if it is not valid, and if sensitization to vasoconstrictor hormones is the correct interpretation, the results should be no better than those observed in "Sam's" left hand. An experiment has recently been carried out to test these two hypotheses:

Monkey "Elsie:" The weight of this animal was 3.48 Kg. On Dec. 12, 1935, through a right axillary incision separating the second and third ribs, the pleura

TABLE 5.—*Observations on Monkey "Elsie," Dec. 31, 1935*

Time	Temperature of Palm at Base of Fingers		Pulse	Rectal Temperature	Room Temperature	Comment
	Right (Denervated)	Left (Control)				
2:30	.....	.....	...	.....	72.0 F.	Taken from animal room
2:40	88.5 F.	82.5 F.	...	.....	.....	
2:45	86.5 F.	80.5 F.	150	.....	.....	
3:00	83.0 F.	76.5 F.	154	101.1 F.	.....	
3:02	.....	.....	...	.....	.....	0.25 cc. of 1,000 solution of epinephrine subcutaneously
3:10	83.0 F.	75.5 F.	208	.....	.....	Shivering hard
3:30	81.5 F.	77.5 F.	195	.....	72.0 F.	No longer shivering
3:50	79.5 F.	76.5 F.	174	.....	73.4 F.	
4:10	79.5 F.	76.5 F.	140	.....	73.0 F.	
4:30	81.5 F.	77.5 F.	144	101.5 F.	73.4 F.	

was opened widely and the thoracic sympathetic chain was dissected free from a point well above the inferior cervical ganglion to below the seventh rib. The animal made an uneventful recovery and presented a warm, dry hand plus a Horner's sign. Nineteen days later she was tested with a similar dose of epinephrine under environmental conditions as close as possible to those of "Sam's" test, with the results shown in table 5.

This table exhibits practically a reduplication of the figures obtained from "Sam's" left hand after cervicothoracic ganglionectomy and proves that many clinical failures after this operation are not due to uncut vasoconstrictor fibers but must be ascribed to vasospasm induced by substances circulating in the blood stream.

COMMENT

Throughout this entire series of experiments one point stands out with striking clarity: that whenever smooth muscle of the arterial walls

is deprived of its nerve supply and the axons have had time to degenerate there results a tremendous increase in sensitivity to the sympathomimetic hormones. This is in line with the behavior of denervated smooth muscle in other organs reported by Rosenblueth and Cannon [24] and the general action of chemical mediators of autonomic impulses. Cannon [25] emphasized that the reaction to the sympathomimetic hormones takes place at a point between the nerve endings and the responsive mechanism in smooth muscle cells, but the exact way in which the contractile substance is affected has not been determined. Although this sensitization phenomenon had been known to physiologists since the original work of the Meltzers [11] and Elliott,[10] its clinical application was not stressed until Freeman, Smithwick and White [15] made their observations on the sympathectomized limbs of patients with Raynaud's disease.

The experiments reported here show that after ganglionectomy sensitivity increases slowly to a maximum during the course of the second week. It develops regardless of whether the vasoconstrictor pathway has been divided in its preganglionic or in its postganglionic portion, but after postganglionic degeneration it is greatly accentuated. While our experiments are rather crude for a quantitative comparison, it is obvious that both in the rabbit's ear and the monkey's hand vasoconstriction in response to epinephrine is from two to three times greater after postganglionic denervation. This difference in sensitivity of smooth muscle has been measured accurately by Hampel,[26] who utilized the nictitating membrane of the cat as an indicator and recorded its isotonic response in centimeters on a smoked drum. Figure 9 from his article shows that, regardless of whether the postganglionic (superior cervical ganglion) or preganglionic (cervical sympathetic trunk lower down) neurons are destroyed, sensitization to epinephrine increases to a maximum at about the twelfth day. After preganglionic degeneration the maximum response amounts to 3.5 cm., but after postganglionic it rises to 8.17 cm. The slow development of sensitization, which occurs pari passu with axonal degeneration, accounts for a somewhat misleading response to diagnostic procaine block. Immediately after the vasoconstrictor nerves have been blocked this phenomenon is absent. Consequently

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24. Rosenblueth, A., and Cannon, W. B.: Studies on Conditions of Activity in Endocrine Organs: XXVIII. Some Effects of Sympathin on the Nictitating Membrane, Am. J. Physiol. **99**:398, 1932.

25. Cannon, W. B.: Chemical Mediators of Autonomic Nerve Impulses, Science **78**:43, 1933.

26. Hampel, C. W.: Effect of Denervation on the Sensitivity to Adrenine of the Smooth Muscle in the Nictitating Membrane of the Cat, Am. J. Physiol. **111**: 611, 1935.

temporary paralysis with procaine may give an exaggeratedly favorable response, although its demonstration that the vessels are free from organic obliterative disease is still valid. This is also true of the other common vasomotor tests, such as the intravenous injection of typhoid vaccine and heating of the body. These tests are sufficiently accurate in the lower extremity, where but slight sensitivity develops to epinephrine, but in the arm the results of cervicothoracic ganglionectomy correspond with the predicted degree of vasodilatation for only a few days.

Grant [27] recently published the results of an investigation into the mechanisms which control the circulation in the rabbit's ear before

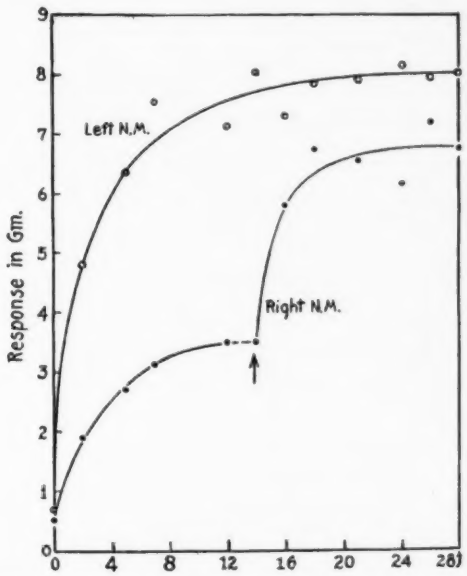

Fig. 9.—Isotonic responses of the nictitating membrane (*N.M.*) of a cat to 1 cc. of a 1:100,000 solution of epinephrine after removal of the left superior cervical ganglion (postganglionic neurons) and section of the right cervical sympathetic trunk (preganglionic neurons). The ordinate represents response in centimeters; the abscissa, days after operation. The right superior cervical ganglion was removed fourteen days after section of the right trunk as indicated by the arrow beneath the lower curve. The chart shows that as the postganglionic neurons degenerated the nictitating membrane on the right became as sensitive to epinephrine as the one on the left. (From Hampel; [22] reproduced with the permission of the *American Journal of Physiology.*)

27. Grant, R. T.: Further Observations on the Vessels and Nerves of the Rabbit's Ear, with Special Reference to the Effects of Denervation, Clin. Sc. **2:** 1, 1935.

and after denervation. The close similarity of the conclusions formulated in England with those that had previously been published by one of us (White [5]) is striking. Figure 10, which is reproduced from Grant's paper, illustrates his measurements of the relative sensitivity of the auricular arterioles to epinephrine after preganglionic and postganglionic denervation. Like us, he concluded that:

> The observations on the rabbit also suggest that the occurrence of Raynaud attacks in man after sympathectomy may be due, at least in part, to a circulating adrenaline-like substance which, as we have seen in the rabbit, is released under conditions of nervous stimulation. Further, if the phenomena of the regain of tone are the same in man as in the rabbit, then it would seem that when operative measures are undertaken for the relief of peripheral vascular disease, preganglionic section is preferable to ganglionectomy, thus reducing the subsequent reactivity of the vessels.

The only difference between our work and that of Grant lies in his statement that bilateral adrenalectomy failed to modify the vaso-

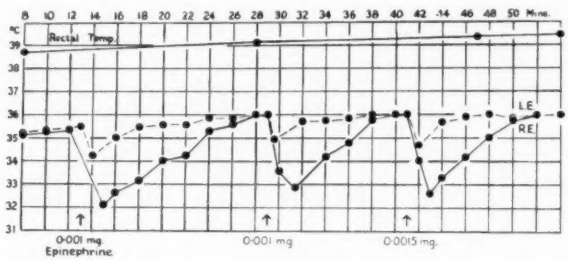

Fig. 10.—The vasoconstrictor effect of epinephrine on a rabbit's ears. *L.E.* represents the response in the left ear, which had been decentralized by cutting the sympathetic trunk below the stellate ganglion. *R.E.* represents the response in the right ear after degeneration of the postganglionic neurons following removal of the superior cervical and stellate ganglia. It is shown that after each of the three injections of epinephrine the vessels of the right ear constricted more strongly than those of the left, and the temperature fell lower. (From Grant; [27] reproduced with the permission of *Clinical Science Incorporating Heart*, London.)

constrictor responses in the sensitized ear. For this reason he spoke of the residual ability of the denervated vessels to go into spasm as due to the secretion of an "adrenaline-like substance" which is secreted during nervous or muscular activity and reduced by rest. Our results after resection of one adrenal gland and denervation of the remaining gland make us think that the reaction is primarily due to epinephrine. This conforms with the findings of Hartman, McCordock and Loder [13] in experiments on the denervated iris of the cat, also with the observations of Cannon, Lewis and Britton [14] on the denervated heart.

Epinephrine is the preponderant hormone secreted when the organism is excited or cold or is performing muscular work (Cannon [28]). We believe it to be the most important secretion in regulating the caliber of denervated arteries, but it is probably not the only one. Sympathin may also play a part, for Newton, Zwemer and Cannon [29] and also Whitelaw and Snyder [30] have shown that it enters the circulation under similar circumstances. In one of our rabbits, which was under anesthesia obtained with pentobarbital sodium, we performed bilateral adrenalectomy and then stimulated the nerves along the hepatic artery to promote the liberation of sympathin (Cannon and Rosenblueth [31]). After a minute the arterial tree of the sympathectomized ear (postganglionic denervation) constricted intensely and remained blanched for two minutes after the stimulus was removed. This experimental observation was not clearcut and requires further verification before definite conclusions can be reached concerning the importance of sympathin. Grant [27] considered the possibility that one of the hormones secreted by the pituitary gland may play a contributing part. In four rabbits from each of which the intrasellar pituitary body had been removed he could detect no visible alteration from the previous responses in either the normal or the denervated ears. We have ruled out any direct rôle of the thyroid secretion by performing total thyroidectomy on two occasions, with negative results.

The final point to be brought out is the relation of chemical control of arterial tone to the unsatisfactory results of the cervicothoracic operation for Raynaud's disease in comparison with the good results of lumbar ganglionectomy. If our experimental observations and their interpretation, which have been corroborated by Grant, are correct, they fit in with the known anatomic arrangement of the vasomotor outflow to the arm and leg in a way which accounts perfectly for the divergent postoperative results in the two extremities. Figure 11 (reconstructed from Langley's [21] work) and our findings after section of spinal roots in monkeys explain why sensitization is so much

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28. Cannon, W. B.: The Wisdom of the Body, New York, W. W. Norton & Company, Inc., 1932.

29. Newton, H. F.; Zwemer, R. L., and Cannon, W. B.: Studies on the Conditions of Activity in Endocrine Organs: XXV. The Mystery of Emotional Acceleration of the Denervated Heart After Exclusion of Known Humoral Accelerators, Am. J. Physiol. **96**:377, 1931.

30. Whitelaw, G. P., and Snyder, J. C.: The Physiological Production of Sympathin in the Liver, Am. J. Physiol. **110**:247, 1934.

31. Cannon, W. B., and Rosenblueth, A.: Studies on Conditions of Activity in Endocrine Organs: XXIX. Sympathin E and Sympathin I, Am. J. Physiol. **104**: 557, 1933.

greater in the area of distribution of the brachial plexus than in that of the sciatic nerve. According to Langley,[32] "the vertebral sympathetic ganglia are segmental and each supplies sympathetic fibers to its own spinal nerve. The few fibres which do not arise from the corresponding ganglion arise from the ganglion next above or below." Thus, the foot (with the exception of a small area around the internal malleolus which is supplied by the saphenous nerve) must derive its postganglionic neurons from the lowest lumbar and the upper three sacral ganglia (the segmental origin of the sciatic nerve). Lumbar ganglionectomy is therefore essentially decentralization and leaves the majority of postganglionic fibers in the sciatic nerve intact (fig. 11). The response to vasoconstrictor hormones is consequently minimal. On the other hand, cervicothoracic ganglionectomy causes degeneration of nearly all the postganglionic fibers to the brachial plexus and maximal sensitization in the digital arterioles (fig. 3).

The practical application of this new physiologic concept indicates that the ganglia which are commonly removed in cervicothoracic ganglionectomy are the most important ones to preserve. Theoretically, it should be possible to decentralize the smooth muscle of the vascular tree in the arm by: (1) section of the anterior thoracic spinal roots; (2) cutting the chain below the second or third thoracic sympathetic ganglion. The first procedure is obviously impracticable, because it would involve laminectomy and rhizotomy over nearly the entire length of the thoracic portion of the spinal cord. The second possibility was first tried two years ago and is proving successful. At the Massachusetts General Hospital, Smithwick[33] has resected a portion of the third rib and cut the chain below its third thoracic ganglion. In order to interrupt any possible preganglionic fibers emerging in the second and third intercostal nerves (above the segmental outflow demonstrated by Langley) he has also resected the proximal 2 to 3 cm. of these nerves and left the ganglia and their blood supply intact. The cephalic end of the chain has been swung up and buried in the intercostal muscles in order to prevent regrowth of nerve fibers across the gap. Fifty upper extremities in thirty-one patients with Raynaud's disease have been submitted to this more physiologic operation. To date the results have been as successful as those in the lower extremity. Sensitization to vasoconstrictor hormones is no greater than in the leg and is insufficient to

32. Langley, J. N.: The Sympathetic and Other Related Systems of Nerves, in Schäfer, E. A.: Textbook of Physiology, New York, The Macmillan Company, 1900, vol. 2, p. 616.

33. Smithwick, R. H.: Modified Dorsal Sympathectomy for Vascular Spasm (Raynaud's Disease) of the Upper Extremity, Ann. Surg. **104**:339, 1936.

cause recurrent vasospasm of clinical significance. Telford [34] has corroborated Smithwick's findings by a slightly different operation. He also has recognized the importance of leaving the stellate with the second and third thoracic ganglia intact, but has used the cervical

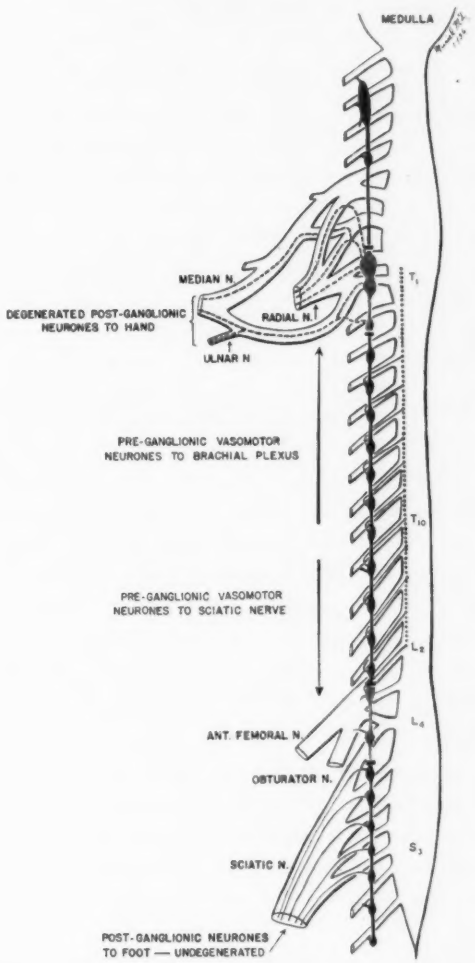

Fig. 11.—The anatomic arrangement of the preganglionic and postganglionic vasoconstrictor neurons to the hand and foot. This shows that the entire postganglionic network to the hand degenerates after cervicothoracic ganglionectomy, whereas resection of the second and third lumbar ganglia interrupts only the preganglionic fibers to the sciatic nerve.

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34. Telford, E. D.: The Technic of Sympathectomy, Brit. J. Surg. **23**:448, 1935.

approach to cut the chain below the third rib and the white rami communicantes to the second and third intercostal nerves. If after these operations regeneration of sympathetic function does not take place (and after a two years' follow-up of Smithwick's cases this seems unlikely) the problem of the surgical treatment of Raynaud's disease in the upper extremity may well be solved.

SUMMARY AND CONCLUSIONS

1. In line with the behavior of unstriated muscle in general, denervated smooth muscle in the arterial walls becomes abnormally sensitive to circulating sympathomimetic hormones as the vasoconstrictor nerves degenerate.

2. The increase in sensitivity is much greater after degeneration of the postganglionic neurons than after destruction of the preganglionic portion of the vasoconstrictor pathway. This has been measured in the rabbit's ear and the monkey's hand as well as in human extremities.

3. The most important hormone which mediates residual vasospasm in denervated arteries appears to be epinephrine. Sympathin and other as yet unknown substances probably play a contributory rôle.

4. In explanation of the inferior results of cervicothoracic ganglionectomy we have shown that this operation causes degeneration of the postganglionic fibers to the brachial plexus and thereby a maximal tendency toward residual vasospasm during exposure to cold, exertion or emotional stress. In contrast, lumbar ganglionectomy interrupts the vasoconstrictor outflow to the sciatic nerve in its preganglionic portion and thereby leaves a minimal residual response to chemical stimuli.

5. Application of these principles to the treatment of Raynaud's disease in the upper extremity is leading to a more physiologic operation, in which the ganglia giving rise to the postganglionic neurons are preserved but the preganglionic connections are cut proximally. This method promises to give as favorable results in the arm as have been achieved in the leg.

HISTOLOGIC STUDIES OF THE BRAIN IN CASES OF FATAL INJURY TO THE HEAD

VI. CYTO-ARCHITECTONIC ALTERATIONS

CARL W. RAND, M.D.

AND

CYRIL B. COURVILLE, M.D.

LOS ANGELES

The possible cause of residual posttraumatic nervous symptoms has long been the subject of discussion. Variance in opinion as to the origin of these manifestations has given rise to two schools of thought. It is held by one school that such symptoms are largely of psychogenic origin and are the direct result of mental and emotional shock incident to the injury. The second group, on the other hand, believe that posttraumatic manifestations are due predominantly to organic lesions of the brain, although the character and distribution of such lesions have not been clearly established. It was our interest in this question that led us to begin what has proved to be a rather prolonged investigation of the changes in the elements of the brain following severe injury. While it is recognized that a study of morphologic changes could scarcely be expected to explain so variable a clinical picture, it was hoped that a more comprehensive and accurate conception of the alterations occurring in the nerve elements would at least enlarge our views in this respect.

As a result of our studies as a whole, an important concept has gradually taken shape—that injuries to the head tend to result in changes in the brain of two types. One of these changes is general and is a result of the force of the blow. The other is more typically local, the location and character of the lesion being a combined result of the mechanism of the injury and the anatomic characteristics of the injured region. To be sure, the dividing line between the two types is not always sharply drawn, but in the main they are sufficiently characteristic to be distinguished one from the other.

The general changes are largely physiologic rather than morphologic, although their effects may become apparent in the cerebral tissues if sufficiently marked. Loss of consciousness following the injury and edema of the brain are examples of this general change. Unconsciousness itself is not accompanied by any recognizable change in the cortical

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nerve cells so far as we can discover and is probably to be explained on the basis of a physicochemical change of reversible character in the colloids of the cell. Generalized impairment of vasomotor control, which results in edema, may become evident if the process is advanced. This is indicated grossly by flattening of the convolutions and decrease in the number and size of the oligodendroglia cells. The facile absorption of tissue fluid by these cells probably protects the parenchyma of the brain from the effects of hydration, whatever these effects may be. The increased amount of free fluid, so characteristic of posttraumatic states, is probably due to increased transudation into the perivascular and subarachnoid spaces and into the ventricles. The increased vacuolation of the choroidal and the ependymal epithelium and the distention of the pericellular and the perivascular spaces are presumed evidences of such activity.

The local effects of injury to the head, resulting in characteristic structural alterations, are to be seen in cases of contusion and laceration of the brain. Within the injured area the cerebral tissue is macerated and disintegrated, the nerve elements being completely destroyed. As a result of removal of the decadent tissue by phagocytosis and repair by the astrovascular elements, a scar is produced. If there has been extensive injury of the overlying dura so that fragments of its tissues have been implanted into the cerebral wound, the scar may contain an abundance of connective tissue. With contraction of this type of scar, local contractures and deformities are likely to result. On the other hand, after a typical contusion the damaged cerebral tissues and intermingled blood clot are removed *en masse* as the clot breaks down, leaving a comparatively smooth-walled defect. Only feeble adhesions to the dura develop at the margin of the wound if the arachnoid is torn, and these are incapable of regional distortion. The injury, therefore, results in loss of function of the nerve elements within the contused area, either directly through the destruction of nerve cells or by interruption of connections of other cells with this area. The loss of this function may not be detected on clinical examination.

MATERIAL AND METHODS OF STUDY

In this phase of our investigation the material used was much more extensive than that utilized in previous studies. The brains of 309 persons with injury to the head have been studied in the Ramón y Cajal laboratory since the original histologic studies were undertaken. Two hundred and twenty-nine instances of cerebral contusion were noted. It was from this group that material was selected for study of the architectonic alterations of the cerebral and the cerebellar cortex after trauma.

For the most part frozen sections were used. The usual staining methods were utilized with success, since we were concerned for the moment only with the disturbance in the arrangement of cells and not with alterations in their structure. At

times the use of metallic methods for the demonstration of nerve fibers and neurofibrils have proved to be of value. The usual methods for the demonstration of Nissl's substance have also proved to be worth while.

In the study of posttraumatic changes in the nerve cells we have chosen to consider the subject under two general headings: (1) changes in the cortical architecture and (2) alterations in structure of the nerve cells. In this report we have limited ourselves to a consideration of the architectonic disturbances, leaving the more detailed changes in the cells for another contribution.

NATURE OF CORTICAL INJURIES

A traumatic lesion of the cortex or subcortex is the composite result of the size and consistency of the injuring agent, the intensity of the force with which it is applied to the skull, the mechanism of its application and the anatomic peculiarities of the affected region. The actual production of the lesion which one sees at operation or at autopsy is the result of both primary and secondary factors. The actual thrust of the convolution against the interior of the skull results in the original bruise, and this effect is primary. This original injury is accompanied by rupture of many local blood vessels, and the resulting hemorrhage plays an important rôle in producing the ultimate lesion, not only in architectural changes but in the chemical reaction of the nerve tissues themselves, as our next study will emphasize.

For our purpose in this connection, cortical lesions may be divided morphologically into three groups: (1) areas of cellular necrosis, (2) contusions and (3) lacerations. The first type of lesion is invariably microscopic; the second may be either microscopic or macroscopic, while the last is invariably a gross injury. Each of these lesions will be considered in turn.

AREAS OF CORTICAL NECROSIS

In the course of previous investigations, the occurrence of small circumscribed acellular or relatively acellular areas was noted.[1] For the most part these areas were observed in the vicinity of cortical contusions and were apparently of vascular origin. Some of them represented areas of focal hemorrhage in which the red cells were not apparent or had disappeared in the evolution of the lesion (fig. 1). In other instances such areas were noted in the vicinity of contusions but were not due to the small accompanying hemorrhages (fig. 2). Their proximity to these hemorrhages, however, suggests a vascular origin.

1. Rand, Carl W., and Courville, Cyril B.: Histologic Studies of the Brain in Cases of Fatal Injury to the Head: IV. Reaction of the Classic Neuroglia, Arch. Neurol. & Psychiat. **27**:1342 (June) 1932. The photomicrograph shown in figure 15 should be noted.

At times such areas occurred in the absence of any evident hemorrhage. In some instances, especially when the subcortical white matter was involved, the lesion was evidently a small infarct. In other cortical lesions these acellular foci resembled the so-called *Herde* described by German investigators.

The etiology and mechanism of production of these areas of cortical necrosis have been a subject of much interest to neurohistologists. They have been observed in a variety of conditions. Perhaps the most helpful studies in their interpretation are those concerned with asphyxia. After

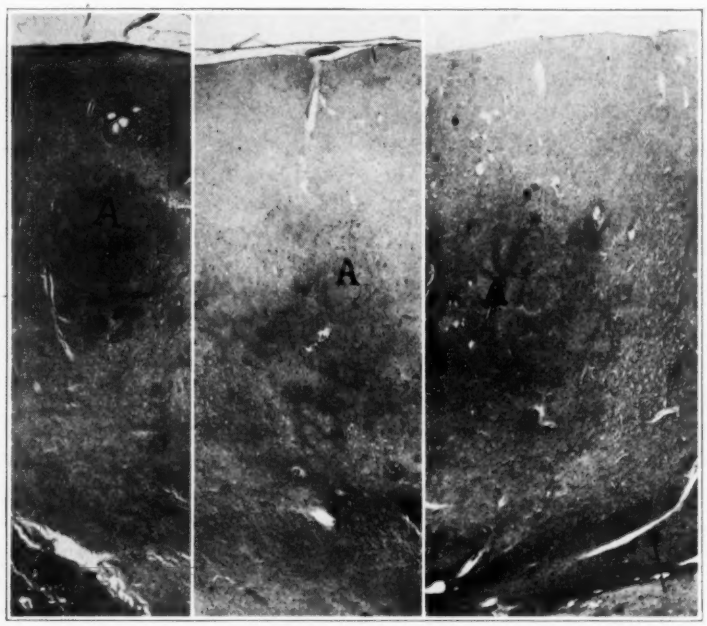

Fig. 1.—Photomicrograph (× 14; hematoxylin and eosin stain) of sections of the cortex, showing discolored acellular areas (*A*), due to grossly invisible petechial hemorrhage. The nerve cells in the margin of the hemorrhage are accentuated, owing to the presence of hematogenous pigment in their cytoplasm.

ligation of the major blood vessels in experimental animals Gildea and Cobb [2] noted these characteristic areas in the cerebral cortex. This seems to indicate that these "acellular" areas are the result of local asphyxia; in fact, they appear to be the characteristic lesion of asphyxia. In a recent study by one of us (C. B. C.),[3] in which sections of the

2. Gildea, E. F., and Cobb, Stanley: The Effects of Anemia on the Cerebral Cortex of the Cat, Arch. Neurol. & Psychiat. **23**:876 (May) 1930.

3. Courville, Cyril B.: Asphyxia as a Consequence of Nitrous Oxide Anesthesia, Medicine **15**:129 (May) 1936.

brain were studied in cases in which there was fatal termination after a respiratory crisis during nitrous oxide anesthesia, these pale areas, affecting one or more of the cellular layers of the cerebral cortex, were almost invariably present. In these cases it has been assumed that this lesion is evidence of asphyxia. On the basis of this assumption it is likely that when this lesion is present it is presumptive evidence of asphyxia, although, to be sure, the actual mechanism of its production is not always clear.

In order to determine more definitely the incidence and character of this interesting lesion so far as its relation to cerebral injury is con-

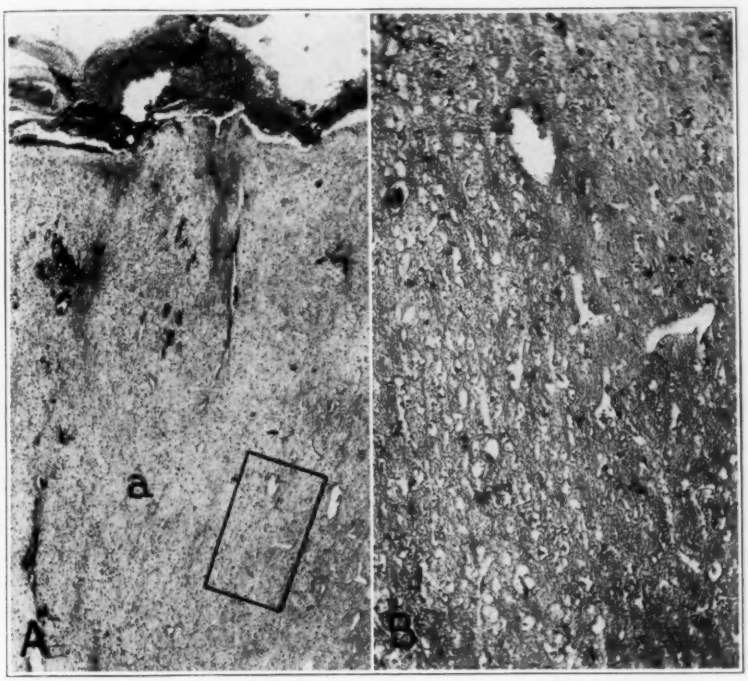

Fig. 2.—Photomicrographs (hematoxylin and eosin stain) showing (*A*) an acellular area (*a*) adjacent to a lesion of cortical contusion, which resembles a focus of cortical necrosis due to asphyxia (× 18), and (*B*) a more detailed view of the margin of the area, showing enlargement of the pericellular and perivascular spaces and sclerotic changes in the nerve cells, which are characteristic (× 65).

cerned, a special study was made of a series of 18 consecutive cases in which an injury to the head had been sustained. Blocks were taken from symmetrical locations in the frontal, parietal, temporal and occipital portions of the cortex, the basal ganglia of the cerebral hemispheres and the cortex of the cerebellar hemispheres. The patients from whom

the tissues were obtained had survived for intervals varying from two and one-fourth hours to seventy-four days. All varieties and degrees of cerebral traumatic lesions were to be observed in the group. In the brain of only one of these patients were areas of cortical necrosis of this type observed.

A Mexican woman, aged 58, had survived the injury for only six and one-fourth hours. She had been struck by an automobile and sustained a small laceration of the right side of the forehead. She was admitted to the hospital in coma and a state of shock, evidently due to fracture of the right humerus and the right tibia.

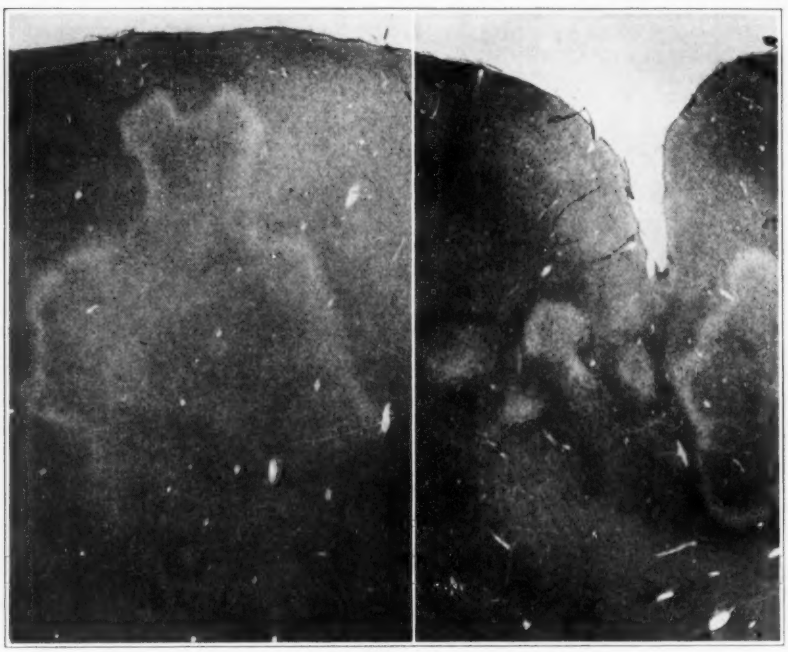

Fig. 3.—Photomicrograph of a section of the cortex showing acellular areas (*Herde*) of unknown origin after injury to the head. (× 14; hematoxylin and eosin stain).

There were also multiple severe lacerations of the abdominal wall and extremities. At autopsy, in addition to the other wounds, generalized severe subdural hemorrhage and a minor subarachnoid hemorrhage, more extensive on the right side, were present. No gross lesions of the brain itself were evident, either externally or internally. On microscopic examination, extensive acellular areas were noted in the cortex of the right temporal and parietal lobes (fig. 3).

The significance of the presence of these areas in the cerebral cortex after injury is not entirely clear. It is evident that they are not a characteristic manifestation of concussion, since they were so rarely observed in our series of cases of injury to the brain. They are, furthermore,

not due to severe cerebral injury, since there was no gross injury to the brain in the case mentioned. They were not universally present but were apparently confined to the right cerebral hemisphere. In discussing the changes of this nature present in the brain in one of their cases, Winkelman and Eckel [4] attributed their presence to edema of the brain, which in turn was due to interference with the blood supply. If these lesions are due to edema they should be observed much more frequently than the results of our special study indicate. It is likely that some additional factor other than the local vascular alteration or the resulting edema must be present to account for their occurrence. In the case of Winkelman and Eckel, as in the case reported in this paper, some degree of shock was present, but more study must be given to the incidence and distribution of lesions of this type after trauma before the etiology can be definitely established.

CORTICAL CONTUSION

Contusion of the cortex may be either a direct or a contrecoup effect of injury. It is probably due to contrecoup in the majority of instances. More rarely it results from a depressed fracture of the cranial vault or base. In this connection we shall limit ourselves to the common contusion of the cerebral cortex, usually due to contrecoup.[5] From an anatomic standpoint one may classify cortical contusions into three essential types: (1) the wedge-shaped contusion, (2) superficial contusion and (3) diffuse contusion. Since the architectural changes in the cortex vary with each type, they will be discussed separately.

Wedge-Shaped Contusion.—Contusion of this type is usually the result of focal injury to the cortex by contrecoup. Its size is dependent on the severity of the injuring force and its location on the direction of force. As a rule it is observed in the subfrontal cortex or in the ventrolateral portion of the temporal cortex. Because of its greater prominence, the ridge of the convolution is predominantly affected. In cross-section the triangular or wedge shape of the injured zone becomes apparent. In the frontal lobe the triangle tends to have a relatively

4. Winkelman, N. W., and Eckel, John L.: Brain Trauma: Histopathology During the Early Stages, Arch. Neurol. & Psychiat. **31**:956 (May) 1934.

5. In this study our primary interest lies in the alteration in the arrangement of the nerve cells of the cerebral cortex. Since, however, when the contusion reaches any magnitude the subcortical white substance is also affected, brief mention will be made of the extension into the subcortex whenever such reference seems germane to the problem at hand.

We have not included other secondary or remote effects of injury to the cortex, such as softening due to vascular occlusion (Courville, C. B., and Olsen, C. W.: Post-Traumatic Cerebral Softening: Delayed Symptoms Suggesting Interval Hemorrhage Following Minor Injury to the Head, West. J. Surg. **43**: 219 [April] 1935).

narrow base, the bruise itself extending deep into the subcortex. On the other hand, in the temporal lobe the outline of this contusion assumes more nearly the shape of an equilateral triangle (fig. 4 *A*).

The essential architectural alterations are dependent on the extent of the original bruise and the amount of hemorrhage. In subfrontal contusion of this type the amount of cortical damage may be small and relatively insignificant. In the temporal lobe, on the other hand, the contusion is relatively more extensive, and large areas of cortex may be destroyed. In minor contusions of this type the affected area is indicated grossly by small shotlike hemorrhages located within the cortex and lying beneath a narrow zone of unaltered cortical tissue. In the

Fig. 4.—(*A*) Photograph showing a small wedge-shaped contusion of the cortex of the third temporal convolution, of about normal size, and (*B*) photomicrograph (× 10; reduced silver method) showing detail of the cortical contusion. Sparing of the subpial glial layer and pallor of the areas of tissue between the hemorrhages are characteristic.

more severe types hemorrhage is more profuse, and the clot approaches the surface, spreads laterally and invades the deeper layers of the cortex. At the margins of a moderately sized contusion there tends to remain an overhang of pia mater and attached subpial cortex, which appears as a hooklike projection on cut section. It may be stated, then, that the type of lesion and the accompanying changes in the cortical architectonics depend essentially on the mechanism of the injury.

In a previous paper in this series [1] the contused area was divided into a number of zones to indicate the reaction of the neuroglia. The

same general plan can be utilized in discussing the effect of injury of this type on nerve cells. There may be considered (1) a central area of immediate destruction, (2) a zone of delayed disintegration and (3) a zone of incomplete injury. The adjoining areas are not permanently injured by the contusion.

Area of Immediate Destruction: In minimal contusion of the cortex this area may consist of one or more separate foci, representing areas of local hemorrhage. The expanding hemorrhage first compresses the adjacent tissue and then destroys it by infiltration and tearing. In a minor injury this process may stop with the formation of several separate and discrete hemorrhages at the point of injury (fig. 4*B*). In this case the ultimate lesion is characterized by the presence of a number of acellular areas, which, after disintegration and absorption of the red cells, may be confused with the *Verödungs* of different etiology.

In the case of a more severe lesion there is confluence of these foci of expanding hemorrhage, resulting in isolation of intervening bits of cortical tissue, with enclosed nerve cells. These small cortical sequestrums, isolated from their source of nutrition and oxygen, soon disintegrate and become intermingled with the blood clot. Even in cases of contusion only a few hours old, the remnants of these isolated sequestrums are difficult to identify. In still more severe lesions no trace of nerve tissue can be observed from the beginning, and this central zone is represented only by the blood clot which occupies the region.

Zone of Delayed or Secondary Disintegration: In cases of contusion only a few hours old the nerve elements immediately adjacent to the focal hemorrhages show little or no morphologic change in preparations made as a routine. In the preparations impregnated by the method of Ramón y Cajal, these elements show an unusual affinity for reduced silver and appear as dark brown or black outlines in the section.[6] In older lesions evidences of degeneration soon make their appearance in respect to both cellular morphologic characters and structure (figs. 5*A* and *B*). This process of delayed degeneration occurs in a narrow zone about the area of hemorrhage. With degeneration of the fibrinous and cellular elements of the clot there remains a cavity surrounded by a narrow and somewhat irregular zone in which the process of necrosis is still taking place. If the cavity communicates with the subarachnoid space by rupture of the overlying pia, evacuation of the decadent thrombus is facilitated to a considerable degree.

6. This phenomenon of preservation necrosis, first described by Ramón y Cajal in experimental wounds of the brain, will be given more attention in our next study concerned with changes in nerve cells. Ramón y Cajal asserted that cells showing this reaction were dead but, because of some property of the blood serum, maintained a strong affinity for reduced silver.

Zone of Incomplete Injury: Adjoining the zone of delayed necrosis is a narrow zone in which injury is less profound and in many cases insufficient to bring about the death of the nerve cell. In dealing with the interstitial elements, this zone has been described as the zone of reversible reaction. This term was used to signify the concept that the cell was not so seriously injured but that recovery might occur. In this zone, however, were observed astrocytes that were morphologically crippled and in which complete recovery was unlikely. These cells, although surviving for some time, probably succumb to regressive

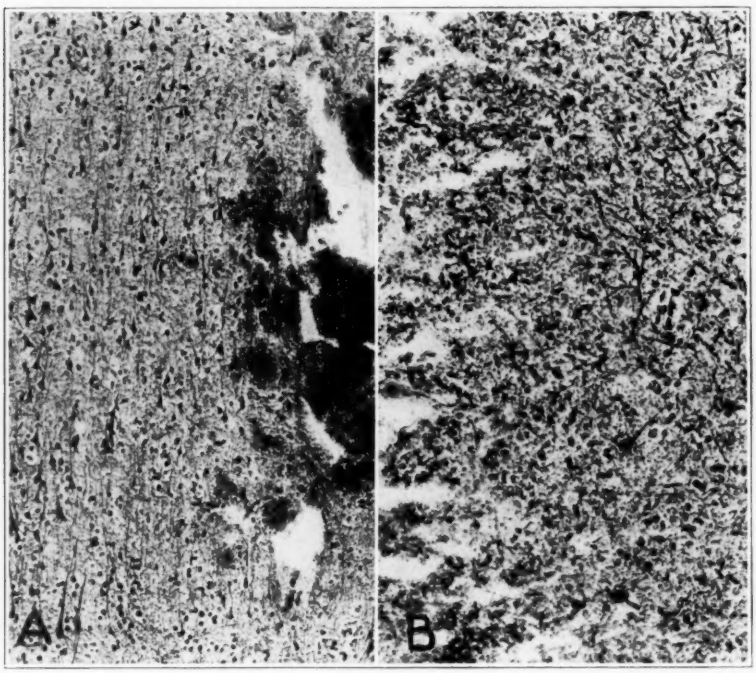

Fig. 5.—Photomicrographs (reduced silver method) showing loss of nerve cells and morphologically altered nerve cells (*A*) in the vicinity of a small cortical hemorrhage (× 80) and (*B*) adjacent to the cortical contusion (× 140).

changes and ultimately disappear. In referring to nerve cells in this zone several possibilities must be considered, although some of them must fall outside the limits of this morphologic study. In this zone, months and even years after injury, crippled nerve cells may be observed, often encrusted with iron.[7] Such cells are probably without function. On the other hand, it may logically be predicated that shortly

7. Courville, Cyril B., and Kimball, T. S.: Histologic Observations in a Case of Old Gunshot Wound of the Brain, Arch. Path. **17**:10 (Jan.) 1934.

after the injury nerve cells in this zone may for the time lose their Nissl substance and undergo changes in the neurofibrillar apparatus and perhaps in other elements of the cytoplasm and nucleus. These cells may sooner or later be capable of regaining incompletely or completely their normal function. These cells may be said to undergo a reversible reaction.

Distal to this third zone the cells undergo no more evident morphologic change than do cells at greater distance from the local injury. In general it may be said that the effect of the injury rapidly decreases

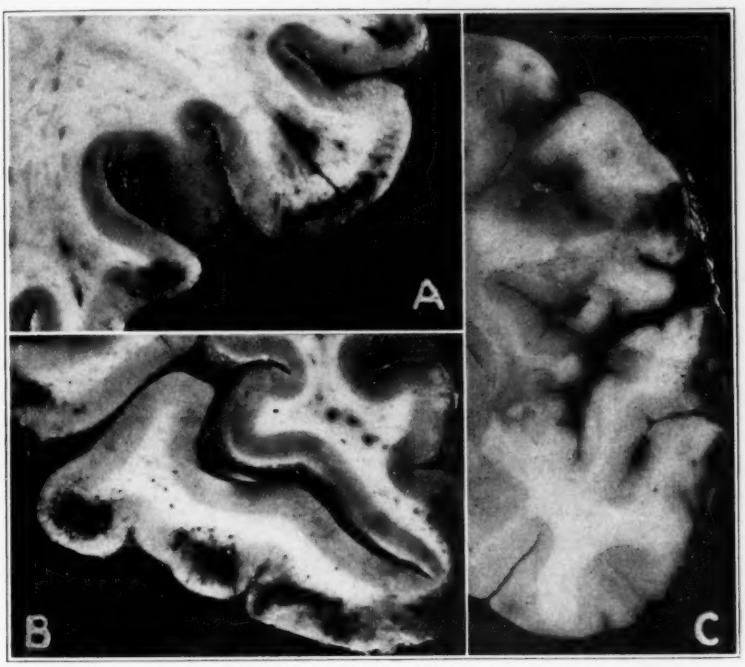

Fig. 6.—Photographs showing superficial contusions (*A* and *B*) in the subfrontal portion of the cortex (× 1⅔) and (*C*) in the temporoparietal portion of the operculum.

as one leaves the margin of the contused area, if the demonstrable morphologic changes in the nerve cells can be taken as a criterion. It is remarkable how close to this margin apparently normal nerve cells can be observed, even after an interval of weeks has passed since the time of injury. This observation lends much weight to the conception that the immediate effect of the original injury is to produce hemorrhage and that this hemorrhage is largely responsible for the extent of cortical damage.

Superficial Contusion.—In contrast to the wedgelike contusion, with its tendency to penetrate the subcortical white substance, is the more widespread superficial and spotlike bruise. It tends to occur where the cortex lies against a gently curving portion of the inner table of the skull, unmarked by convolutional depressions or other irregularities. It may be observed on the basilar surface of the frontal lobe or on either side of the sylvian ridge but is particularly frequent in the opercular and lower portion of the parietal cortex (fig. 6). In these cases severe disintegration of the entire cortex is unusual, even in widespread

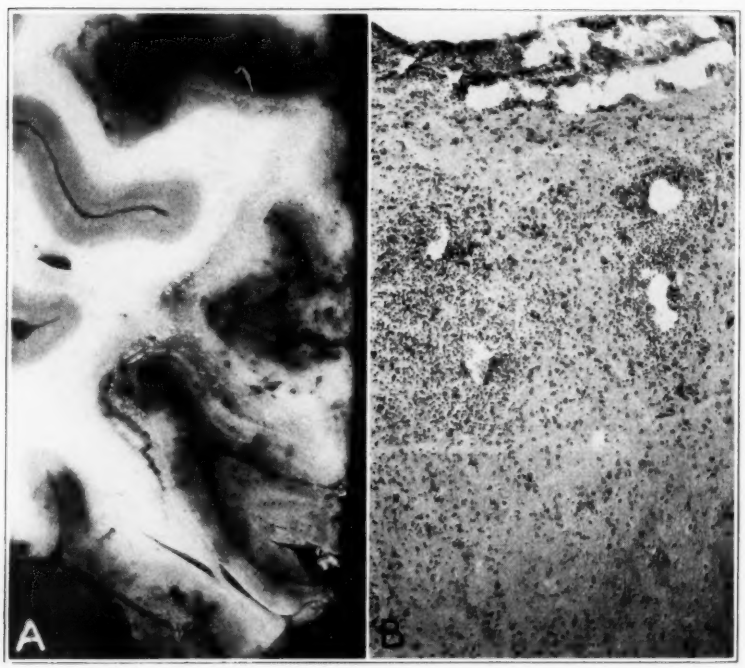

Fig. 7.—(*A*) Photograph (× 1⅔) showing diffuse cortical contusion of the occipital lobe, and (*B*) photomicrograph (× 80; hematoxylin and eosin stain) showing petechial hemorrhage and loss of nerve cells in a diffuse occipital contusion.

lesions. The essential lesion is again a shotlike or streaked hemorrhage, particularly affecting the upper layers of the cortex. In the average case the focal hemorrhages tend to become confluent, giving rise to a mottled or spotty appearance. In the more severe types, but probably not in persons who survive an injury, there occurs at times widespread disintegration of the superficial layers of the cortex. This gives the surface of the brain a "greasy feel" on postmortem examination.

In a lesion of this type the cyto-architectonic change resembles that of minor cortical contusion in other situations. The cells in the immediate region of the enlarging hemorrhage are destroyed. About each separate hemorrhage there occurs a narrow zone of delayed disintegration and reversible change, much more limited in extent than the zone about the larger lesion. The zone about the smaller hemorrhage may not be demonstrable histologically. As the red cells disintegrate, clear local areas remain, which may resemble superficially the *Verödungs* of other etiology. The two lesions should not be confused at this stage. In severe lesions the superficial layers of the cortex at the crest of the convolutions of the affected region may be disintegrated, but, as previously stated, it is unlikely that this occurs in the patient who recovers.

Diffuse Cortical Contusion.—As has been emphasized in another contribution,[8] contusions of the posterior portion of the temporal and the occipital lobe, because of the peculiar anatomic situation, are likely to be diffuse and at times extensive. The arrangement of the cortex is more or less completely disrupted, owing primarily to the large number of focal hemorrhages and secondarily to the impairment of nutrition and tissue respiration incident to the interruption of the blood supply. Large portions of the cortex may undergo complete disintegration in an irregular fashion. In these areas there is more or less complete loss of the nerve cells. These cells soon lose their affinity for stains, and the cortex appears to be devoid of them. Their presence may be demonstrated, however, with the metallic methods. The underlying subcortex is likewise softened and has a yellowish, spotted appearance, due to the occurrence of larger and usually more discrete petechial hemorrhages. Owing to the presumed impairment of circulation, the entire cortex tends to detach itself from the underlying white substance, much as it does in hemorrhagic softening due to venous thrombosis. The essentials of cyto-architectonic change in this lesion are shown in figure 7.

CEREBELLAR CONTUSION

Contusion of the cerebellum is relatively less common. It is usually the result of linear fracture of the occipital bone which runs parallel with the midline, extending into or terminating in the region of the foramen magnum. Rarely it may occur as the result of compound comminuted and depressed fractures of the occipital bone or from forcible contact with the tentorium. It is rarely extensive and seldom affects the subcortex. As a rule the superficial folia are more seriously affected.

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8. Courville, Cyril B.: Diffuse Cortical Contusion of the Occipital Lobe, Arch. Path. **20**:523 (Oct.) 1935.

In cases of minimal contusion of the cerebellum gross examination may show only a few minute foci of hemorrhage and at times nothing. In such instances microscopic sections may show a few infiltrated wandering cells and focal hemorrhage in the molecular layer (fig. 8 *A*). The Purkinje cells may show no changes whatever. As Winkelman and Eckel [4] have indicated, these areas may be multiple. In the more severe conditions the molecular layer may show considerable infiltration with hemorrhage and resultant necrosis of the tissue. When the lesion is even more severe the superficial portion of the folium may be disin-

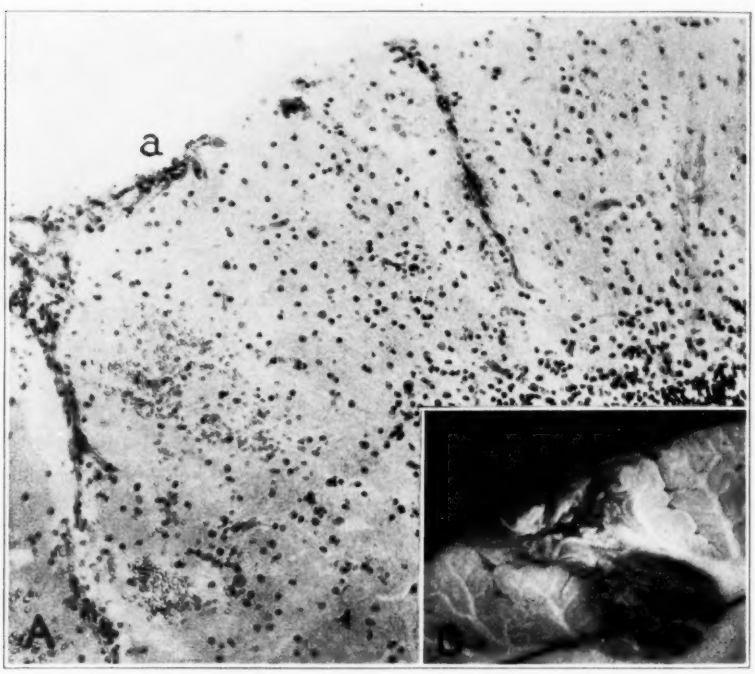

Fig. 8.—(*A*) Photomicrograph (× 120; hematoxylin and eosin stain) showing minimal contusion of the cerebellar cortex. Focal effusions of erythrocytes are shown in the superficial portion of the molecular layer. (*B*) photograph (× 1⅔) indicating superficial foliar contusion and staining of the deeper portions of the cortex, with hemorrhage.

tegrated so that the layer of Purkinje cells is likewise affected. The contusion extends like a wedge into the underlying cortex, much as it does in the case of contusion of the temporal lobe (fig. 8 *B*).

LACERATION OF THE CORTEX

Laceration of the cerebral cortex may be primary or secondary. Primary laceration is due to direct injury of the cortex by an indriven

foreign body or bony fragments. The subcortical white substance is almost invariably injured as well. Secondary laceration is the result of escape of blood to the exterior from an underlying intracerebral hemorrhage. We are not concerned with the second type, even though the hemorrhage which caused it may be of traumatic origin.

So far as the architectural characteristics are concerned, laceration presents certain major points of difference from contusion. These differences suggest the possible alterations which may be observed in the arrangement of the nerve cells in a lesion of this type. The wound

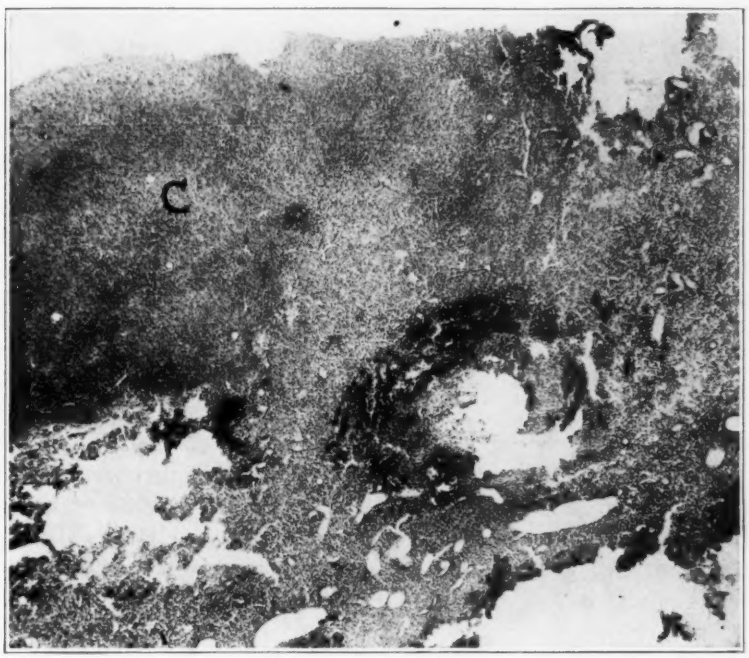

Fig. 9.—Photomicrograph of a section through the margin of an area of contused laceration, showing undermining of the adjacent normal cortex (*C*), × 18; hematoxylin and eosin stain.

is of irregular outline and results in greater destruction of cortical and subcortical tissue than is consequent to contusion. Hemorrhage may be more abundant, since larger cortical vessels may be interrupted. The indriven foreign bodies also aggravate the lesion. The dura is frequently lacerated, and the presence of dural fragments also tends to alter the local tissue reaction.

The essential alterations in cyto-architectonics lie largely in the irregularity of the lesion produced and in the nature of the resulting reaction (fig. 9). The development of the various zones is essentially

the same as in contusion, but the zones show greater irregularity in their margins and variability in width. The more extensive and irregularly distributed foci of hemorrhage, as well as the irregular manner in which the lesion is produced, contribute to the formation of a ragged wound. Groups of nerve cells are likely to be isolated within areas of necrosis. They may be separated from their own and other axons by undercutting of the cortex due to the trauma itself. Such cells are functionally useless, even though they are morphologically sound. These architectural alterations are an early effect and are due to the mechanism by which the wound is produced.

The later architectural changes which are characteristic of severe laceration, with associated injury to the dura, are the result of formation of a scar of connective tissue. It is this type of cortical distortion that has been described by Foerster and Penfield[9] as a result of war wounds of the brain and which they asserted is responsible for the epileptiform attacks which occur frequently in such instances. By the gradual contraction of the scar the adjacent cortex is pulled toward the site of the original wound. The astrocytes tend to assume a radiating arrangement, pointing toward the center of the scar. We have had the opportunity to study but one case of this type; in this instance the time interval was not sufficient to permit the development of a strong scar of connective tissue. A lesion of this type is exceptional after traffic accidents.

SUMMARY AND CONCLUSIONS

Alterations in nerve cells following trauma to the head include: (1) disturbance in their normal arrangement and (2) changes in their structure. Since problems concerning each of these phases differ so widely, only the first has been considered in this paper. Alterations in nerve cells will be the subject of a forthcoming study.

Cyto-architectonic alterations due to cortical contusion and laceration were studied in 39 cases. A study of focal necrosis was made in an additional series of 18 cases. Various details of contusion have been studied in a total of 229 cases.

In the areas of cortical necrosis (*Herde, Verödungs*) the changes are probably due to deprivation of oxygen, although the exact mechanism of their production is not known. The lowering of the blood pressure incident to shock may be a contributing factor.

In contusion of the brain the force of the blow is responsible for hemorrhage into the cortex as well as for the bruise itself. Hemorrhage is responsible to a great extent for the architectural alterations resulting from such a lesion.

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9. Foerster, O., and Penfield, W.: The Structural Basis of Traumatic Epilepsy and Results of Radical Operation, Brain **53**:99, 1930.

Nerve cells are able to maintain their morphologic identity remarkably near the margin of a contusion. Crippled nerve cells may be present in partially disorganized areas for months and years after the injury.

Three zones of action are to be observed in the injured cortex: (1) a zone of immediate and complete destruction of nerve elements, (2) a zone of delayed disintegration and (3) a zone of incomplete and at times recoverable injury. In the last zone nerve cells which may be morphologically crippled may survive for years. Other cells, more distantly removed, may undergo certain minor structural changes capable of complete recovery.

Cyto-architectonic changes resulting from laceration of the cortex may be considered as primary, or early, and secondary, or late. The primary changes, due to the immediate effect of the traumatizing agent, are characterized by irregular contour of the areas of degeneration and variable width of the marginal zones. The late alterations, resulting from the pull of the scar on the adjacent cortex, are of variable degree, dependent on the amount of connective tissue and the extent of its adhesion to the dura.

PRIMARY MYOPATHIES

REPORT OF THIRTY-SIX CASES AND REVIEW OF THE LITERATURE

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SAN FRANCISCO

Recent favorable therapeutic reports [1] have revived interest in the muscular dystrophies. A brief historical review, however, revealed that this condition has been recognized at least for over a century. Bell [2] in 1830 first described cases in which the disease resembled pseudohypertrophic muscular dystrophy; Meryon,[3] Duchenne,[4] Erb [5] and Landouzy and Dejerine [6] greatly advanced knowledge of the subject through clinical and postmortem observations. It remained for Erb,[7] however, to give the first clear conception and differentiation of the myopathies. Shortly thereafter, Batten [8] suggested the following classification, which I have employed in this study:

1. Simple atrophic type (Leyden-Moebius) (amyotonia congenita)
2. Pseudohypertrophic type (Duchenne)
3. Juvenile type (Erb)
4. Facioscapulohumeral type (Landouzy-Dejerine)
5. Distal type (Gowers and Spiller)
6. Myotonia atrophica
7. Mixed and transitional types

From the Department of Pediatrics, the University of California Medical School.

1. (*a*) Milhorat, A. T.; Thomas, K., and Techner, F.: Significance of Creatine in Progressive Muscular Dystrophy and Treatment of the Disease with Glycine, Proc. Soc. Exper. Biol. & Med. **28**:609, 1932. (*b*) Tripoli, C. J.; McCord, W. M., and Beard, H. H.: Muscular Dystrophy, Muscular Atrophy, Myasthenia Gravis and Strabismus, J. A. M. A. **103**:1595 (Nov. 24) 1934.

2. Bell, Charles: The Nervous System of the Human Body, ed. 2, London, Longman and others, 1830, p. 160.

3. Meryon, cited by Ingbert, C. E.: Pseudohypertrophic Muscular Atrophy, J. Nerv. & Ment. Dis. **34**:1, 1907.

4. Duchenne, G. B.: Recherches sur la paralysie musculaire pseudo-hypertrophique ou paralysie myo-sclérosique, Arch. gén. de méd. **1**:5, 1868.

5. Erb, W.: Ueber die juvenile Form der progressiven Muskelatrophie, Deutsches Arch. f. klin. Med. **34**:467, 1884.

6. Landouzy, L., and Dejerine, J.: De la myopathie atrophique progressive, Rev. de méd. **5**:81, 1885.

7. Erb, W.: Dystrophia musculorum progressiva, Deutsche Ztschr. f. Nervenh. **1**:173, 1891.

8. Batten, F. E.: The Myopathies or Muscular Dystrophies, Quart. J. Med. **3**:313, 1909-1910.

To this list Spiller [9] would have added the true hypertrophic type. These forms have the common characteristics of being familial or hereditary and usually progressive and developing early in life. Such a classification is convenient for descriptive purposes, but the types must be regarded as manifestations of the same disease entity. Between them are many forms that cannot be sharply demarcated, which serve to show their close interrelationship. The inclusion of amyotonia congenita in the group of simple atrophic forms is controversial, as some regard it as a type in itself. Whether the distal type of Gowers is a true dystrophy is also disputed, but both Batten [8] and Spiller [9] stated that it is a primary myopathy. It differs from the peroneal form of atrophy (Charcot-Marie-Tooth type) in that there are no peripheral sensory changes, facial involvement is not uncommon, and although atrophy begins in the distal parts, it soon spreads beyond them and the muscles of the trunk may be affected. In my series 16 cases were of the atrophic type, 16 of the pseudohypertrophic, 1 of the facioscapulohumeral, 1 of the distal and 2 of the mixed or transitional.

The frequency of the occurrence of this disease is difficult to estimate. Hough [10] stated that it occurs in about 6 of 100,000 of the population and comprises about 1 per cent of all cases of orthopedic disease.

CHARACTERISTICS OF THE MYOPATHIES

Age.—The primary myopathies usually develop in infancy or early childhood. The disease may arise, however, at any time from birth to adult life. Gowers,[11] who reported 220 cases collected from the literature, found that in cases of the worst involvement the disease began before the sixth year. In an analysis of 95 cases, Hough [12] noted that the signs were observed before the age of 2 years in 12.5 per cent of the instances, after 2 and up to 4 years in 50 per cent and between the ages of 5 and 7 years in 30 per cent. Voshell,[13] discussing the pseudohypertrophic form, stated that the age of onset is between 2 and 8 years, with the average at 4 years. In 5 of the cases in my series signs were noted almost from birth; in 6 cases the disease began at the age of less

9. Spiller, W. G.: The Relation of the Myopathies, Brain (pt. 1) **36**:75, 1913.

10. Hough, G. de N., Jr.: Progressive Pseudohypertrophic Muscular Dystrophy, J. Bone & Joint Surg. **13**:825, 1931.

11. Gowers, W. R.: Pseudohypertrophic Muscular Paralysis, London, J. & A. Churchill, 1879.

12. Hough, G. de N., Jr.: Progressive Pseudohypertrophic Muscular Dystrophy: Results of Treatment with Epinephrine and Pilocarpine, J. A. M. A. **101**: 2113 (Dec. 30) 1933.

13. Voshell, A. F.: Progressive Pseudohypertrophic Muscular Dystrophy, South. M. J. **26**:156, 1933.

than 1 year, in 19 cases between 1 and 5 years and in 6 cases before 10 years. Thus, in over 80 per cent the onset was before the fifth year of life.

Race.—Dystrophies have been described in persons of almost all races. The statement that the pseudohypertrophic form affects only the white race cannot be accepted, since authentic cases of this type have been described in Negro children.[14]

Sex.—All authors are agreed that boys are more often affected than girls. In Gowers'[11] series 190 cases occurred in boys and 30 in girls. In Hough's[12] series of cases of the pseudohypertrophic type there were no girls, and 48 of the 49 patients in the series of Mettel and Slocum[15] were boys. Gordon[16] stated that 5 of 6 cases of the pseudohypertrophic type occurred in boys and cases of the atrophic type were equally divided between the sexes. Approximately 75 per cent of the cases in my series were in boys, with only 1 case of the pseudohypertrophic form occurring in a girl.

Hereditary and Familial Influence.—Minkowski and Sidler,[17] from studies in Switzerland, concluded that in the Duchenne type inheritance of the disease occurs as a recessive mendelian character. The Landouzy-Dejerine type exhibits mendelian dominance. In 20 of the 50 cases reported by Collins and Climenko[18] hereditary aspects were shown. In the series of Mettel and Slocum[15] 30 per cent of 49 patients showed a definite hereditary influence. A strong familial incidence was recorded by Gowers,[11] who found 118 cases in 39 families. Poore[19] reported a familial incidence in 43.5 per cent of 85 cases of pseudohypertrophic muscular paralysis. After tracing the genealogical history of 15 families, Weitz[20] concluded that muscular dystrophy is a heredofamilial degeneration. A familial incidence is shown in 15 (42 per cent) of the cases in my series.

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14. Pearson, K.: Two New Pedigrees of Muscular Dystrophy, Ann. Eugenics **5**:179, 1933.

15. Mettel, H. B., and Slocum, Y. K.: Pseudohypertrophic Muscular Dystrophy, J. Pediat. **3**:352, 1933.

16. Gordon, W.: Muscular Dystrophies, Lancet **1**:759, 1923.

17. Minkowski, M., and Sidler, A.: Klinische und genealogische Untersuchungen zur Kenntnis der progressiven Muskeldystrophie, Arch. d. Julius Klaus-Stiftg. f. Vererbgsforsch. **3**:239, 1927-1928.

18. Collins, J., and Climenko, H.: Clinical Study of Fifty Cases of Muscular Dystrophy, Contrib. Sc. Med. & Surg., 25 anniv. founding of New York Post-Grad. M. School & Hosp., 1908, p. 360.

19. Poore, C. T.: Pseudo-Hypertrophic Muscular Paralysis, with an Analysis of Cases, New York M. J. **21**:569, 1875.

20. Weitz, W.: Ueber die Vererbung bei der Muskeldystrophie, München. med. Wchnschr. **69**:100, 1922.

Particularly interesting are 2 instances (cases 20 and 23) in which the condition seemed to have been directly transmitted by the mother, even though she was unaffected herself. Such examples have been cited also by Tscherning [21] and Funsten.[22]

Pathogenesis and Pathologic Changes.—A more detailed discussion of these changes will be given in another report. Briefly, the hypotheses of etiology may be summarized as follows: (1) the disease is primary in the muscles; (2) it is secondary to nervous disturbances; (3) it arises from involvement of the endocrine system, or (4) it is caused by trauma or infection.

There is still considerable controversy about the pathologic characteristics. The changes in the muscles, as noted in specimens taken from 8 of my patients, consisted of atrophy, occasionally of hypertrophy, of the muscle fibers, with vacuolation, splitting and loss of transverse striations. Proliferation of the nuclei, replacement by fat, increased fibrous connective tissue and vascular hyperplasia were observed.

Changes in the anterior and lateral horn cells of the spinal cord, consisting either of atrophy or of diminution in the number of cells, have been described (Holmes [23] and Gil [24]). Infrequently, cellular changes have been noted in the midbrain, medulla and pons (Westphal [25] and Henke and Seeger [26]). I believe, however, that there is no evidence of a degenerative process in the nervous system in the majority of patients with muscular dystrophy.

Symptomatology.—The onset is usually insidious, although the sudden initiation of symptoms after trauma or infection has been noted. Paresis, involving particularly the proximal muscles of the extremities, slowly progressing to paralysis is the outstanding feature. Involvement of the muscles of the pelvis and thigh, and of the erector spinae muscles results in the peculiarity of gait and difficulty in mounting stairs which is so typical of patients with this disease. The patient falls readily and in arising literally "climbs up his legs." Lordosis, scoliosis and "pot

21. Tscherning, R., cited by Mills, H. P.; Haines, T. H., and Sessions, Mina: Familial Muscular Dystrophy: Studies of Six Cases in One Family, Arch. Neurol. & Psychiat. **11**:43 (Jan.) 1924.

22. Funsten, R. V.: Muscular Dystrophy, J. Bone & Joint Surg. **5**:190, 1923.

23. Holmes, G.: On the Spinal Changes in a Case of Muscular Dystrophy, Rev. Neurol. & Psychiat. **6**:137, 1908.

24. Gil, J. M. J.: Ueber die Befunde am zentralen Nervensystem bei der Dystrophia musculorum progressiva, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **35**: 116, 1933.

25. Westphal, A.: Weiterer Beitrag zur Frage "Dystrophia musculorum propressiva und extrapyramidaler Symptomenkomplex," Klin. Wchnschr. **6**:198, 1927.

26. Henke, K., and Seeger, S.: Ueber die Vererbung der myotonischen Dystrophie, Ztschr. f. d. ges. Anat. (Abt. 2) **13**:371, 1927.

belly" are frequent. If the muscles of the shoulder girdle are attacked there is a forward drooping of the shoulders, so that the scapulae become prominent. "Falling through the shoulders" results when an attempt is made to raise the patient by the axillae. Localized atrophy or hypertrophy appears in the course of the disease. The tendon reflexes are usually diminished or abolished. Naccarati [27] reported a case in which there were exaggerated knee jerks but no other evidence of involvement of the pyramidal tract. This condition was seen in 1 of the patients (case 16) in my series. This Naccarati attributed to increased irritability of the substance of the motor nerve ending, which with further involvement would entirely disappear. Fibrillary tremors and the reaction of degeneration are almost always absent. Spiller,[9] however, stated that both features have been observed in cases of true dystrophy. In both instances of the mixed type in our series (cases 31 and 33) fibrillary twitchings were shown, but in all other respects the findings resembled those in the primary myopathies. Implication of the muscles innervated by cranial nerves other than the seventh has been reported. Ptosis has been observed by Landouzy and Dejerine and atrophy of the tongue by Reinhold.[28] Later, as the disease progresses, contractures occur in the muscles opposed to the atrophic groups, and marked deformities result. Cerebral phenomena, such as intellectual impairment, have been recorded and occurred in over 30 per cent of the cases reported by Mettel and Slocum. Twenty per cent of the patients in my series were so affected.

Trophic changes have been reported often. Pigmentary changes, asphyxia and scleroderma have all been found in association with the dystrophies.[28a] Schultze,[29] Spiller [9] and others have described marked thinning of the bones, such as was noted in patient H. S. (case 33, fig. 1). A peculiar moth-eaten appearance of the epiphyses of the femur was noted in another instance (case 16) in my series. Otherwise, roentgenograms showed only generalized atrophy of the bone attributed to disuse.

The relationship between the ductless glands and the primary myopathies remains unsettled. Cases have been described in which the disease

27. Naccarati, S.: Primary Myopathies, New York M. J. **105**:351, 1917.

28. Reinhold, H.: Ueber einen ungewöhnlichen Fall von myopathischer Muskelatrophie mit Beteiligung des Gesichts, und bulbärer Muskelgebiete und negativem Befund am Nervensystem, Ztschr. f. Nervenh. **4**:189, 1893.

28a. Roger, H.: Myopathie facio-scapulo-humerale a forme scléreuse, Rev. neurol. **35**:408, 1919.

29. Schultze, F.: Ueber Combination von familien progressive Pseudohypertrophie die Muskeln mit Knochenatrophie, Deutsche Ztschr. f. Nervenh. **14**:459, 1898-1899.

was associated with thyroid disturbance (Boveri [30]), involvement of the pituitary gland (Eulenberg [31]), changes in the pineal gland, producing roentgen shadows (Timme [32]), parathyroid insufficiency (Rathery and his associates [33]) and pluriglandular signs (Brock and Kay [34]). I have noted enlargement of the thyroid, a small sella turcica, undescended testes and adiposogenital dystrophy. However, I believe that these changes are too infrequent to permit the assumption of an endocrine disturbance as the cause of muscular dystrophy.

Cardiovascular changes, such as labile and rapid pulse rate, extrasystoles and slurred first sound, have been noted by me. Boas and Lowenburg [35] demonstrated persistent tachycardia, and Berblinger and Duken [36] showed paroxysmal ventricular tachycardia with the electrocardiograph. Pathologically, myocardial changes similar to those in skeletal muscle have been recorded.[37] That the blood pressure is usually within normal limits was shown by Boas and Lowenburg.[35]

Anemia, eosinophilia and leukocytosis with lymphocytosis have been reported, but I observed no characteristic blood picture. The sedimentation time was normal. Urinalysis revealed occasionally a trace of albumin and acetone, but in the majority of cases the findings were normal. Examination of the spinal fluid showed no alteration. The basal metabolic rate was inconsistent, varying from minus 36 per cent to plus 35.5 per cent in this group.

Blood Chemistry.—Hypoglycemia and delayed utilization of dextrose have been reported by Janney and his collaborators [38] and by McCrudden

30. Boveri, P.: De la névrite hypertrophique familiale, Semaine méd. **30**:145, 1910.

31. Eulenberg, A.: Ueber einen schweren Fall infantiler familiärer Muskeldystrophie mit osteoarthropischen Deformationen, Deutsche med. Wchnschr. **22**: 458, 1896.

32. Timme, W.: Progressive Muscular Dystrophy as an Endocrine Disease, Arch. Int. Med. **19**:79 (Jan.) 1917.

33. Rathery, F.; Mollaret, P., and Waitz, R.: Myopathie myotonique avec signe de Chvostek: Étude humorale. Rôle de l'insuffisance parathyroïdienne, Bull. et mém. Soc. méd. d. hôp. de Paris **54**:395, 1930.

34. Brock, S., and Kay, W. E.: Study of Unusual Endocrine Disturbances: Their Associated Myopathies, Endocrine Balance and Metabolism Findings, Arch. Int. Med. **27**:1 (Jan.) 1921.

35. Boas, E. P., and Lowenburg, H.: The Heart Rate in Progressive Muscular Dystrophy, Arch. Int. Med. **47**:376 (March) 1931.

36. Berblinger and Duken, J.: Der kardio-intestinale Symptomenkomplex bei der progressiven Muskeldystrophie, Ztschr. f. Kinderh. **47**:1, 1929.

37. Globus, J. H.: Pathologic Findings in Heart Muscle in Progressive Muscular Dystrophy, Arch. Neurol. & Psychiat. **9**:59 (Jan.) 1923.

38. Janney, N. W.; Goodhart, S. P., and Isaacson, V. I.: The Endocrine Origin of Muscular Dystrophy, Arch. Int. Med. **21**:188 (Feb.) 1918.

and Sargent.[39] However, hypoglycemia is not a constant feature (Bramwell[40] and Hughes and Shrivastava[41]); again there is not always delayed utilization of dextrose, it being even rapid in some cases (table). For the present, all that can be said is that there is altered carbohydrate metabolism in the majority of patients with dystrophy.

The blood showed normal values for nonprotein nitrogen, urea, carbon dioxide content, calcium, phosphorus, potassium, lactic acid, cholesterol, creatine and creatinine. Previously, Janney and his colleagues[38] and Mosberg[42] had noted a lowered creatinine content of the blood,

Fig. 1 (case 33).—Roentgenogram showing coarse trabeculation at the ends of the femurs and in the bones of the pelvis. The long bones appear as thin pipe-stems.

39. McCrudden, F. H., and Sargent, C. S.: Hypoglycemia and Progressive Muscular Dystrophy, Arch. Int. Med. **17**:465 (April) 1916.

40. Bramwell, E.: Muscular Dystrophies, Sympathetic System and Endocrine Glands, Lancet **2**:1103, 1925.

41. Hughes, T. A., and Shrivastava, D. L.: Carbohydrate Tolerance in Two Cases of Muscular Dystrophy, Indian J. M. Research **15**:437, 1927.

42. Mosberg, G.: Beitrag zur Kenntnis des Stoffwechsels der Dystrophia musculorum progressiva, Klin. Wchnschr. **9**:2051, 1930.

while McCrudden and Sargent [39] reported hypocholesteremia. Tests with epinephrine and insulin gave normal results. The amount of chlorides was slightly reduced in 2 cases, and abnormal salt tolerance and retarded excretion of salt were demonstrated. It is interesting that 1 patient (case 31) experienced temporary subjective improvement after several months on a diet rich in salt.

As shown by many other investigators,[43] there are excess creatinuria, diminished creatinine output and an almost quantitative excretion of ingested creatine, varying with the severity of the condition. After therapy with amino-acetic acid there is increased creatinuria, which falls after several weeks but may never reach the level present before therapy. Milhorat and his associates [1a] stated that creatinuria is augmented after such therapy, but Brand and Harris [43a] could not substantiate this. I have noted a slight increase in urinary creatinine in a few cases.

The excessive creatinuria following ingestion of amino-acetic acid has been suggested as a differential point between the primary and the secondary myopathies. However, Nevin [44] has shown recently that the increased excretion of creatine following administration of amino-acetic acid also occurs in cases of muscular atrophy.

Examination of muscle tissue has shown histologic improvement after amino-acetic acid therapy, according to Reinhold and his co-workers.[45] In 6 of their 8 specimens a better quality was shown, in 1 a poorer and in 1 no change. One of our specimens showed no obvious changes, and the other, progression in spite of therapy (fig. 2). Analysis of muscles verified the decreased content of creatine and creatinine reported by Reinhold.

Prognosis.—The earlier the onset of the disease the more rapid is the course. After puberty it advances more slowly, and adult life may be reached, but usually with marked muscular weakness and deformity. Hough,[12] in an analysis of 95 cases, found 35 per cent of the patients unable to walk after the age of 5 years and 50 per cent disabled at the age of from 8 to 9 years. Many die near puberty of infections of the respiratory tract. Of 32 patients I was able to trace 10 are dead; in 20 the condition has progressed (9 are bedfast), and in 2 the disease apparently has been arrested.

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43. (*a*) Brand, E., and Harris, M. M.: Further Studies on the Administration of Glycine in Muscular and Neuromuscular Diseases, J. Biol. Chem. **100**:20, 1933. (*b*) Milhorat, Thomas and Techner.[1a]

44. Nevin, S.: A Study of the Muscle Chemistry in Myasthenia Gravis, Pseudohypertrophic Muscular Dystrophy and Myotonia, Brain **57**:239, 1934.

45. Reinhold, J. G.; Clark, J. H.; Kingsley, G. R.; Custer, R. P., and McConnell, J. W.: Effects of Glycine (Glycocoll) in Muscular Dystrophy with Especial Reference to Changes in Structure and Composition of Voluntary Muscle, J. A. M. A. **102**:261 (Jan. 27) 1934.

Chemical Determinations on Patients with Muscular Dystrophy *

Case	Name	Sex	Age	Blood Chemistry: Creatine, Mg.	Creatinine, Mg.	Chlorides Whole Blood, Mg.	Chlorides Plasma, Mg.	Calcium, Mg.	Phosphorus, Mg.	Lactic Acid, Mg.	Dextrose Tolerance, Mg. per 100 Cc.: Fasting	½ Hr.	1 Hr.	2 Hr.	3 Hr.	Urinalysis (24 Hr. Specimen): Creatine, Mg.	Creatinine, Mg.	Nitrogen, Gm.	Comment
1	D. K.	M	10 yr.	3.8	1.0	...	...	....	...	....	92	210	271	82	55	...	...	....	Sedimentation time 300 sec.; B.M.R. 8.8%
2	C. E.	M	8 yr.	...	...	...	...	....	...	....	108	...	...	...	...	...	...	....	Sedimentation time 180 sec.
3	H. L.	M	3 yr.	...	1.1	...	...	....	...	....	85	115	170	94	91	...	...	....	Sedimentation time 45 sec.
4	F. M.	F	13 yr.	4.6	1.3	...	612	11.1	3.6	....	91	154	117	74	...	...	...	....	B.M.R. +9.4%
5	H. M.	M	11 yr.	4.1	1.4	...	622	....	3.9	....	89 98	116	123	86	...	...	...	....	Carbon dioxide content 47.8%; B.M.R. +35.6%
6	F. F.	M	11 yr.	2.8	2.7	...	...	....	...	....	71 71	80 160	147 101	80 (epinephrine test, 0.7 cc. of sol.)	68	...	...	....	Plasma cholesterol 149 mg.
7	M. H.	F	9 yr.	...	...	...	...	....	...	....	103	168	172	119	79	...	...	....	B.M.R. 12%
8	P. C.	F	4 mo.	...	1.5	...	...	....	...	....	71	...	...	...	...	...	...	....	Serum albumin 3.6 mg.; serum globulin 1 mg.; nonprotein nitrogen 13.5 mg. per 100 cc.
9	D. S.	M	16 mo.	4.2	1.0	...	...	11.2	5.0	....	..	...	...	...	...	768	577	....	
10	P. C.	F	4½ yr.	5.3	1.2	...	...	....	...	....	94	130	97	86	76	...	...	....	
11	J. T.	F	7 mo.	4.2	1.4	...	...	....	...	....	90	115	101	83	68	94 Control infant 3	31 16	....	Spinal fluid normal; B.M.R. 30%
12	R. L.	..	11 mo.	...	...	332	...	11.0	2.6	....	..	...	...	...	...	...	...	....	Carbon dioxide content 42.7%
13	C. W.	F	13 yr.	3.9	1.1	...	...	....	...	....	74	101	119	100	105	578	274	....	Muscle creatine 200 mg. per 100 cc.; muscle creatinine 55 mg. per 100 cc.; urine acetone +
																257	432	....	Amino-acetic acid 5 Gm. daily for 3 mo.
																141	340	....	Amino-acetic acid 5 Gm. daily for 11 mo.
																417	338	3.92	1 mo. after discontinuing amino-acetic acid therapy
14	P. A.	M	10 yr.	...	1.2	...	...	....	...	....	99 83	148 133	124 161	111 104	86	...	...	....	Nonprotein nitrogen 48 mg. per 100 cc.; urea nitrogen 9.3 mg.; tuberculin reaction ++
15	M. L.	M	11 yr.	...	...	425	...	....	...	....	..	...	...	...	...	...	...	....	

16	A. D.	M	7 yr.	...	1.1	442	512	....	...	15.1	97	138	148	111	105	...	...	....	Urea 20.6 mg.; potassium (serum) 19.8 and 22 mg.; B.M.R. +35.5% and +9.7%
						406					91	129	144	83	69†				
						459	517						Lactic Acid			939	1,548	12.65	Gastric analysis: free hydrochloric acid 46 degrees; total acid 96 degrees
										24 Hr. Chloride Excretion, Gm.	12.6	17.9	20.1	12.6	12.2†			Ammonia nitrogen 0.77 Gm.	
						405	549	15 Gm. salt		8.39						470	535	....	Trace of albumin in urine; amino-acetic acid 12 Gm. daily for 8 mo.
						428	554	added daily		9.45						348	422	....	Amino-acetic acid 12 Gm. daily for 12 mo.
						483	561	for 3 days		12.70									
						Sodium Chloride Tolerance Test (2.5 Gm. Sodium Chloride)													
										Serum Potassium, Mg.	Urine Chlorides, Gm.								
				Fasting		424.0	566.9			22	0.166								
				½ hr.		424.7	572.8				0.095								
				1 hr.		424.7	572.8				0.207								
				3 hr.		387.9	554.9			20	0.384								
17	C. S.	M	9 yr.	4.9	1.3	...	570	....	...	....	97	166	122	97	76	...	...	....	
												3 Units Insulin							
											83	148 (modified test)	76	83					
18	A. C.	..	11 yr	3.8	1.1	484	...	11.1	5.3	10.9	95	143	133	100	77	1,304	446	....	B.M.R. −23%; nonprotein nitrogen 21.4 mg. per 100 cc.; potassium 24.4 mg.; plasma cholesterol 129 mg.; muscle creatine 125 mg. per 100 cc.; muscle creatinine 52 mg. per 100 cc.
																492	190	....	Amino-acetic acid, 12 Gm. daily for 5 mo.

* The methods used in the chemical determinations appeared in the following articles:

1. Sugar (micromethod)—Hagedorn, H. C., and Jensen: Biochem. Ztschr. **135**: 46, 1923; (micromethod of Folin and Wu)—Folin, O.: J. Biol. Chem. **82**: 83, 1929.
2. Cholesterol—Bloor, W. R.: J. Biol. Chem. **24**: 227, 1916.
3. Creatine and creatinine (Folin-Wu): Hawk, P. G., and Bergeim, O.: Practical Physiological Chemistry, ed. 10, Philadelphia, P. Blakiston's Son & Co., 1931, p. 421.
4. Blood chlorides—Van Slyke, D. D.: J. Biol. Chem. **58**: 53, 1923.
5. Potassium: Breh, F., and Gaebler, O. H.: J. Biol. Chem. **87**: 81, 1930.
6. Lactic acid—Friedemann, W. G., and others: J. Biol. Chem. **52**: 263, 1922.
7. Urine chlorides (Volhard and Arnold) Hawk, P. G., and Bergeim, O.: Practical Physiological Chemistry, ed. 10, Philadelphia, P. Blakiston's Son & Co., 1931, p. 839.
8. Urine creatine (Folin-Benedict-Myers method)—Benedict, F. G., and Myers, V. C.: Am. J. Physiol. **18**: 397, 1907.
9. Urine creatinine (Folin)—Hawk, P. G., and Bergeim O.: Practical Physiological Chemistry, ed. 10, Philadelphia, P. Blakiston's Son & Co., 1931, p. 833.
10. Nonprotein nitrogen—Folin, O., and Wu, H.: J. Biol. Chem. **38**: 81, 1919.
11. Calcium (Clark-Collip modification)—Clark, E. P., and Collip, J. P.: J. Biol. Chem. **63**: 461, 1925.
12. Phosphorus—Fiske, C. H., and Subbarow, Y.: J. Biol. Chem. **66**: 375, 1925.
13. Plasma phosphatase—Kay, H. D.: J. Biol. Chem. **89**: 235, 1930.
14. Serum albumin and serum globulin (Greenberg)—Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 1, p. 693

Chemical Determinations on Patients with Muscular Dystrophy—Continued*

Case	Name	Sex	Age	Blood Chemistry: Creatine, Mg.	Creatinine, Mg.	Chlorides Whole Blood, Mg.	Chlorides Plasma, Mg.	Calcium, Mg.	Phosphorus, Mg.	Lactic Acid, Mg.	Dextrose Tolerance Mg. per 100 Cc.: Fasting	½ Hr.	1 Hr.	2 Hr.	3 Hr.	Urinalysis (24 Hr. Specimen): Creatine, Mg.	Creatinine, Mg.	Nitrogen, Gm.	Comment
19	O. D.	M	12 yr.	...	...	398	...	10.3	5.2	12.6	91	142	149	117	95	920	490	7.8	B.M.R. +24.9%; nonprotein nitrogen 23.9 mg. per 100 cc.; potassium 22.4 mg.; plasma cholesterol 166 mg.; total base 136 milliequivalents per liter; gastric analysis: no free hydrochloric acid, total acidity 20 degrees
											88	111	119	100	71†				
											Lactic Acid								
											8.1	12.9	13.3	10.2	9.4†				
One month after liver therapy						380	...	11.7	5.1	....	..	...	...	...	...	...	...	....	Plasma cholesterol 143 mg.; nonprotein nitrogen 47 mg. per 100 cc.; potassium 22.1 mg. per 100 cc.; gastric analysis: no free hydrochloric acid, total acidity 32 degrees

Sodium Chloride Tolerance Test (2.5 Gm. Sodium Chloride)

	Whole Blood Chlorides, Mg.	Plasma Chlorides, Mg.	Serum Potassium, Mg.	Urine Chlorides, Gm.
Fasting	380	483.3	22.3	
10 min.	399.8	513.2		1.035
½ hr.	405.8	489.3		0.052
1 hr.	381.9	509.6		0.086
3 hr.	330.6	417.7	23.1	1.075
15 Gm. salt added	376	507		6.08
to diet daily for	398	530		14.25
3 days	424	501		9.63

Two months high salt diet (5 Gm. added daily) plus dilute hydrochloric acid 30 drops daily)																			
				5.5	1.0	426	511	....	...	15.1	111	133	166	125	74	...	...	....	B.M.R. +24.9%; nonprotein nitrogen 30 mg. per 100 cc.; cholesterol (plasma) 154 mg.; carbon dioxide content 64.3%

20	T. W.	M	14 yr.	5.4	1.2	430	...	12.0	5.6	13.2	91	138	118	80	70	...	...	....	Cholesterol (plasma) 152 mg.; potassium 23.7 mg. per 100 cc.; nonprotein nitrogen 23.1 mg. per 100 cc.
											97								
											94	(½ hr. after 2 cc. of extract of adrenal cortex intramuscularly)							
											98	(1 hr.)							
											93	(2 hr.)							
21	H. S.	M	10¾ yr.	4.1	1.1	...	...	....	...	....		93.8	97.4	115	129.8	126	226	124	....	B.M.R. 36%
																	580	159	....	1 mo. after 5 Gm. amino-acetic acid daily
																	755	238	....	4 mo. after 12 Gm. amino-acetic acid daily
																	640	220	....	6 mo. after 12 Gm. amino-acetic acid daily
22	N. R.	M	8¾ yr.	5.3	1.0	...	...	....	...	....	..	...	...	...	...	...	329	199	....	Sedimentation time 145 sec.
																	324	221	....	2½ mo. after 12 Gm. amino-acetic acid daily
23	E. S.	F	6 yr.	4.0	1.2	...	533	10.5	5.2	....	109	142	110	112	133	313	250	....	B.M.R. 9%
								10.4	5.3		112	198	177	145	171				
24	B. W.	F	11½ yr.	3.2	1.2	449	...	....	...	....	83	122	115	72	68	242	199	....	Phenolsulfonphthalein test 71%
											86	187	174	95	54‡	522	567	....	After 500 mg. each of creatine and creatinine
				12 Gm. amino-acetic acid for 6 wk.															
				3.0	1.5											209	172	....	After 11 injections of 1 cc. anterior pituitary
																356	286	....	2 mo. after 100 Gm. gelatin daily and 12 Gm. amino-acetic acid daily for 6 wk.
																324	221	....	12 Gm. amino-acetic acid daily for 2 mo.
25	A. L.	M	2 yr.	...	...	...	...	....	...	....	..	...	...	...	...	709	670	....	

† Reaction to test with 0.5 cc. of solution of epinephrine hydrochloride.
‡ Two months after administration of 100 Gm. of gelatin daily.

Treatment.—I have used almost all the glandular products, with no apparent benefit. Carbohydrate, calcium and other medicaments have not yielded results. On the basis of the theory of a nutritional disturbance, Parhon and Savini [46] fed preparations of fetal muscle and reported improvement in 2 cases, but no further reports are available. Kuré and Okinaka [47] expressed the belief that the basic disturbance in

Fig. 2 (case 1).—Photomicrograph of tissue from the gastrocnemius muscle taken for biopsy after two months of amino-acetic acid therapy. The fibers are swollen and degenerated, and there is loss of normal striations. This specimen showed slight progression of the process, as compared with one taken before administration of amino-acetic acid.

46. Parhon, C. J., and Savini, E.: Essais de thérapeutique biologique dans les myopathies primitives, Rev. neurol. **28**:1215, 1914.

47. Kuré, K., and Okinaka, S.: Behandlung der Dystrophia musculorum progressiva durch kombinierte Injektionen von Adrenalin und Pilokarpin, Klin. Wchnschr. **9**:1168, 1930.

muscular dystrophy is an alteration of the autonomic nervous system, and they advocated the use of from thirty to fifty injections daily or on alternate days of from 0.2 to 0.3 cc. of a 1 : 1,000 solution of epinephrine hydrochloride and from 0.1 to 0.2 cc. of a 1 per cent solution of pilocarpine hydrochloride. My limited experience with this therapy agrees with that of Hough, who after a study of 38 cases concluded that the treatment caused symptomatic benefit and might slow the rate of progress but did not cure the disease or alter the mortality.

Opinion regarding the value of amino-acetic acid is divided. Milhorat [1a] and Tripoli [1b] and their co-workers reported definite improvement. Brand [48] reported no striking benefit with amino-acetic acid therapy in 46 cases of muscular dystrophy. Boothby,[49] Steindler [50] and Cheney [51] expressed the same opinion. I have treated 12 patients with from 4 to 30 Gm. of amino-acetic acid daily for from six to twenty-five months. Subjective improvement occurred in 7 cases (58.3 per cent). There were increase in appetite, a gain in weight and a feeling of well-being, and the patient apparently could do more because of the decreased fatigability of the muscles involved. No paresthesias were noted in this group. At the time of writing, the condition seems to be arrested in 2 patients; in 2 others the course has apparently been slowed; 1 died while receiving treatment, and the others have received no appreciable benefit.

How amino-acetic acid acts is still unsettled. It is believed that in muscular dystrophy there is inability to retain creatine in the muscles. Within the body the amino-acetic acid forms creatine, which after a time is retained in the muscles, and coincidentally clinical improvement is evidenced. Furthermore, amino-acetic acid increases the specific dynamic action of proteins, with cystine forms glutathione, which is important in tissue oxidation, and also has a sparing effect on nitrogen and sulfur metabolism. This stimulation of metabolism with amino-acetic acid accounts for the subjective improvement in these patients.

In addition to other therapy, local treatment of the muscles by massage, physical therapy and orthopedic procedures should not be neglected.

SUMMARY AND CONCLUSIONS

The primary myopathies are reviewed. The nature and course of progressive muscular dystrophy are such, I believe, that the use of amino-acetic acid causes no striking improvement in the majority of cases,

48. Brand, E.: Congenital Anomalies of Metabolism with Special Reference to Cystinuria and Myopathies, Bull. New York Acad. Med. **10**:289, 1934.

49. Boothby, W. M., in discussion on Tripoli, McCord and Beard.[1b]

50. Steindler, A., in discussion on Hough.[12]

51. Cheney, C. O., in discussion on Tripoli, McCord and Beard.[1b]

particularly if the condition has begun in early life. Continuation of this therapy, however, is warranted because of the subjective improvement promoted and the possibility that the progress of the disease may be slowed or arrested. Thirty-six cases of primary myopathy are reported briefly.

SUMMARY OF REPORTS OF CASES

CASE 1.—N. R., a boy aged 8¾ years, fell downstairs at the age of 16 months and after this became less active. The calf muscles became prominent, in spite of progressive weakness. He became bedridden three weeks before admission to the clinic. Examination showed atrophy of the muscles of the shoulder girdle and thighs; the ankle jerks were hyperactive, but the other reflexes were absent. Speech was slow and monotonous. The mental age was 5¼ years. After administration of 12 Gm. of amino-acetic acid daily for two months there were gain in weight and subjective improvement but no change in the affected muscles. Biopsy of specimens of muscle obtained before and after therapy revealed no definite changes. At the time of writing, after seven months, progression seems to have been slowed.

CASE 2.—E. R., a boy aged 9 years, a brother of N. R. (case 1), at 14 months began to walk with a waddling gait and to stumble. After an attack of chickenpox at 2½ years, he was unable to walk without aid. He presented atrophy of the proximal muscles of both the upper and the lower extremities; the deep reflexes were absent, and there was bilateral equinovarus. The condition has been slowly progressive, and he is bedridden at present.

CASE 3.—J. R., a boy aged 11 years, a brother of the patients just described (cases 1 and 2) had the same condition as his brothers (fig. 3). The patient started to walk at 11 months but never walked alone. At 18 months he had a febrile illness, with convulsions, and after this progressive wasting was noted. There developed marked right dorsal scoliosis, bilateral equinus and flexion contractures of the hips and knees. Gastro-enteritis caused the patient's death at the age of 14 years.

CASE 4.—T. S., a boy aged 10, when 9 years old was struck in the left thigh by a playmate; one month after this he began to walk with a limp. At the same time his grip became weaker. The calf muscles seemed enlarged. He was given a diet low in carbohydrates for several months and lost considerable weight. The weakness progressed, and he became unable to raise his arms. For the past month he had had pain in the calves. Administration of gelatin, 100 Gm. daily, caused subjective improvement, but the condition slowly progressed. Use of 16 Gm. of amino-acetic acid daily for four months failed to influence the course of the disease.

CASE 5.—A. P., a boy aged 4 years, whose maternal aunt was mentally deficient, had pertussis at 8 months, after which strabismus developed and he became inactive. He was never able to stand unsupported. He suffered a fracture of the left ulna one week before coming to the clinic. Examination showed mental retardation, with bilateral weakness of the external rectus muscles and generalized muscular weakness; all the deep reflexes were diminished, and there was bilateral equinus. Progression of the disease has continued.

CASE 6.—H. L., a boy aged 15 years, had had numerous infections in early childhood. At 2 years he had both scarlet fever and chickenpox, which supposedly left a cardiac lesion. Difficulty in walking, with numerous falls and typical

"climbing up the legs," was noted at about 4 years of age. The calves became prominent, while the other muscles wasted. He became bedridden after an appendectomy at 10 years of age. The physical findings were as follows: pigeon breast, left dorsolumbar scoliosis, generalized wasting, abolition of all deep reflexes, flexion contractures of the knees and elbows and bilateral equinovarus. The first heart sound was slurred. The condition has been slowly progressive. Constipation is troublesome.

CASE 7.—W. C., a boy aged 16 months, since birth had had displacement of the head posteriorly and to the right. He failed to gain well and did not sit up

Fig. 3 (cases 2 and 3).—Photograph of brothers, aged 9 and 11 years, respectively, with a moderately advanced stage of the condition, showing muscular wasting and contracture deformities.

till 1 year of age. One month before his admission to the clinic, the right upper extremity became limp. Examination revealed generalized muscular flaccidity, with diminished deep reflexes and paresis of the right upper extremity. Bronchopneumonia developed which proved fatal. Postmortem examination showed atrophy of the skeletal muscles, reduction in the number of cells of Clarke's column and slight gliosis and lymphocytic infiltration of the anterior horn cells, particularly in the cervical and thoracic regions. No endocrine changes were noted.

CASE 8.—P. A., a boy aged 10 years, did not walk until 3 years of age, and then with a waddling gait. Progressive weakness developed; he fell frequently and arose by "climbing up the legs." He became bedridden at 7 years of age. Physical examination showed that the thyroid gland was palpably enlarged, the face was edematous and the gastrocnemius muscles were hypertrophied. Roentgenograms of the skull and long bones revealed normal structure. The mental age was 4 years and 2 months. The course of the disease has been progressive.

CASE 9.—A. M., a girl aged 20 months, had a brother who died at the age of 6 weeks and was said to have been small and weak and a sister who died at the age of 14 months, of "birth paralysis." The patient never sat up or attempted to stand. Infections of the respiratory tract were frequent. She was well nourished, with a rather large head, dorsal kyphosis, protruberance of the abdomen, generalized flaccidity and absence of reflexes. Urinalysis showed a trace of acetone and diacetic acid. Examination of the spinal fluid gave normal results, as did roentgenograms of the skull and long bones. The further course of the disease could not be traced.

CASE 10.—C. M., a boy aged 14 years, with a brother who died at 7 years of age of the same condition from which the patient suffered, had weakness of the muscles of the shoulder girdle at 1 year of age. Walking was delayed to 3 years of age, and the gait was waddling. After an attack of pneumonia two years prior to examination, the patient had been confined to bed. He showed vasomotor excitability, right dorsal scoliosis, "pot belly," absence of the deep reflexes of the lower extremities and diminution of the upper, contractures of the elbows and hips and bilateral equinus. The electrical reactions were diminished, but there was no reaction of degeneration. The further course of the illness is not known.

CASE 11.—M. H., a boy aged 7 years, had an aunt on his father's side who was mentally defective; the father was addicted to the use of alcohol. Difficulty in walking was noted at 18 months. Increasing muscular weakness resulted in frequent falls. Peculiarity of speech was present since the patient was 2½ years of age. He had frequent infections, including most of the exanthemas, and two attacks of pneumonia. Examination showed bilateral ptosis, paresis of the extraocular muscles, impaired hearing on the left, a thick, furrowed tongue, wasting of the muscles of the shoulder girdle, absence of the deep reflexes of both the lower extremities and of the left upper extremity and diminution of the other reflexes. Examination of the spinal fluid and roentgenograms of the skull revealed nothing abnormal. The further course is unknown.

CASE 12.—R. L., a boy aged 11 months, had two sisters with myopathy, who died at 9 months and 4 years, respectively, of disease of the respiratory tract. The patient was delivered by version and extraction and suffered a fracture of the right clavicle at birth. He never sat up or attempted to stand. He had laryngitis at 3 months and pneumonia and empyema at 9 months. Examination showed a large, flabby baby, with frontal bossing; the erector spinae muscles were weak; the chest was rachitic; the left testicle was undescended, and atrophy of the gluteal muscles and hypermobility of all the joints were noted. The deep reflexes were abolished, and the electrical reactions were greatly diminished. The sella turcica was normal, but the long bones appeared atrophic. Pneumonia developed, and the patient died at the age of 2 years.

CASE 13.—M. L., a boy aged 11 years, had a brother 26 months old who had a condition similar to the patient's and could not walk alone. The patient did not walk till 2½ years of age, and then with a wide base and forward inclination.

Progressive weakness had necessitated rest in bed since one year prior to examination. The patient was emaciated, except for the prominent calves. He had left internal strabismus and an apical systolic murmur. The mental age was 3 years and 8 months. The course of the disease was slowly progressive, and the patient died of an infection of the respiratory tract at 14 years.

CASE 14.—A. L., a boy aged 2 yeara, a brother of M. L. (case 13), had never stood or walked. Examination showed general muscular weakness, which was most marked in the lower extremities, diminution of the deep reflexes and enlargement of the calves. Despite administration of 8 Gm. of amino-acetic acid daily for seventeen months, the condition has slowly progressed.

CASE 15.—C. W., a girl aged 13 years, had been under observation from birth. At 15 months a waddling gait was noted. She began to fall and showed a manner of rising typical of muscular dystrophy. The physical findings were as follows: internal strabismus, lumbar lordosis, "pot belly," knock knees and marked weakness of the thigh muscles, but no apparent atrophy. Administration of 9 minims (0.55 cc.) of solution of epinephrine hydrochloride daily for months did not prevent slow progression of the disease. The upper extremities became involved. Oral administration of adrenal substance (2 grains [0.129 Gm.] daily) gave subjective improvement temporarily. Contractures of the hamstring muscles developed. Administration of Koehler's adrenal extract (3 capsules daily) for five weeks had no effect. Injections of extract of adrenal cortex (1 cc. of solution twice a week) for two months caused a gain in weight and lessened fatigability. Pneumonia developed at the age of 7 years, and at 8 years bilateral dislocation of the hips was shown by roentgenogram. The patient began to complain of pain in the hips, and dorsolumbar scoliosis developed. She was placed under treatment with 5 Gm. of amino-acetic acid daily, which produced subjective improvement and questionable objective results. However, after about twenty-five months with this therapy, there has been slight progression of the disease, but the downward course seems to have been slowed.

CASE 16.—F. M., a girl aged 13 years (fig. 4), whose mother had always had difficulty in walking, had a brother with the same condition as the patient. Development was normal up to the age of 9 years, when she began to lose weight and became progressively weaker. She showed generalized muscular atrophy, cervical adenopathy, a palpable spleen, right dorsal scoliosis, lumbar lordosis and diminished deep reflexes of the upper extremities, but hyperactive knee jerks. The intelligence quotient was 115. Roentgenograms showed a moth-eaten appearance of the neck of the left femur. Injections of 0.5 cc. of solution of epinephrine hydrochloride, with administration of 30 grains (1.94 Gm.) of calcium lactate daily for a period of several months were without any beneficial effect. The patient is now 22 and is markedly deformed.

CASE 17.—H. M., a boy aged 11 years (fig. 4), the brother of the patient in case 16, was well until the age of 5 years, when he began to limp and the muscular power gradually decreased, so that he became bedridden a few months before admission to the clinic. On examination he was morose and sullen. He had carious teeth, general lymphadenopathy, a palpable liver and spleen, absence of deep reflexes, except the achilles, which was sluggish, and bilateral equinovarus. The mental age was 7 years and 10 months (the intelligence quotient was 71). Roentgenograms of the bones showed no abnormalities. Epinephrine hydrochloride (0.5 cc. of solution by injection) and calcium lactate (30 grains [1.94 Gm.]) were given daily for several weeks, and then epinephrine was administered by mouth for several months. At the age of 20 the patient is bedridden and incapacitated.

Case 18.—C. E., a boy aged 8 years, had always been irritable and suffered from enuresis. He did not walk until 26 months of age and then waddled. Weakness, particularly of the lower extremities, progressed, so that there were difficulty in climbing stairs and frequent falls. He became bedridden four months before his admission to the clinic. Blepharospasm, atrophy of the shoulder and pelvic girdle, hypertrophy of the calves, extrasystoles and bilateral equinus were noted. The mental age was 3 years and 10 months. A roentgenogram of the skull revealed normal structure. The patient was given daily 3 cc. of solution of epinephrine hydrochloride orally with 45 grains (2.91 Gm.) of calcium lactate

Fig. 4 (cases 16 and 17).—Photographs of a brother and sister with a severe advanced stage of the atrophic type of muscular dystrophy.

and injections of 0.0006 Gm. of atropine sulfate, with temporary subjective improvement, but later progression of the disease continued. Six months of amino-acetic acid therapy (4 Gm. daily) and eleven months of administration of pilocarpine hydrochloride (1/60 grain [0.0011 Gm.]) and epinephrine hydrochloride (3 minims [0.18 cc.] of a 1:1,000 solution) failed to check the downward course of the disease.

Case 19.—H. L., a boy aged 3 years, had a sister who died at 2 years of age of a condition similar to his. The mother was mentally defective. The patient sat up at 6 months of age, but one month later he became "weak" and

unable to sit up as before. He never walked. Incontinence of urine persisted from birth. The teeth decayed early. The patient was malnourished, with atrophy particularly involving the muscles of the shoulder and pelvic girdles. Speech was indistinct, and a tumor of the tongue was noted. All the deep reflexes were absent, and there were a right varus and a left valgus deformity. The intelligence quotient was normal. The patient died of an infection of the respiratory tract.

CASE 20.—F. F., a boy aged 11 years, whose mother was twice married and whose half-brother had the same condition as the patient, was prematurely born and weighed 4½ pounds (2,041 Gm.) at birth. After pneumonia at 9 months of age he became unable to hold up his head as before. Walking was delayed until he was 2 years of age, and the gait was waddling, with frequent stumbling. On arising he "climbed up his legs." For the past two years he had had cramping pains in the leg muscles. He became bedridden five months before. Prominent calf muscles, lumbar lordosis, wasting of the thigh and arm muscles, absence of knee jerks, diminished ankle jerks and bilateral varus deformity of the feet were the physical findings. The intelligence quotient was 42. He is now bedridden and badly deformed.

CASE 21.—M. H., a girl aged 9 years, developed normally until 4 years of age, when she began to have difficulty in climbing stairs and complained of weakness in the lower extremities. During the following two years she gained 30 pounds (13.6 Kg.) in weight. Intercurrent infections were frequent. The patient was obese, weighing over 90 pounds (40.8 Kg.), and had carious teeth, a palpably enlarged thyroid, dry, coarse skin, lumbar lordosis and a waddling gait. The skull and long bones showed no changes. The mental age was 11 years and 4 months. The patient was given thyroid, ½ grain (0.324 Gm.), and whole pituitary, 3 grains (0.194 Gm.) daily for nine months, with an antiobesity diet. The course was progressively downward, and the patient died suddenly apparently of a cardiac attack. Autopsy, however, was not permitted.

CASE 22.—D. B., a boy aged 7 years, did not walk until 22 months of age and always had a peculiar gait. He fell frequently and arose by "climbing up his legs." For the past year the patient had had cramps in the legs. Examination showed large calves, atrophy of the thigh muscles, diminution of the deep reflexes and absence of the abdominal reflexes. At 15 years of age, the patient is bedridden and has become obese.

CASE 23.—C. S., a boy aged 9 years, whose mother had twice been married, had a half-brother aged 2 years with enlargement of the calves and weakness of the muscles. The mother and the mother's aunt had "goiter." The patient had frequent attacks of bronchitis in infancy. At 5 years of age he fractured the left femur and was in bed for three months. Six months later it was noted that he had a waddling gait and difficulty in arising. The leg muscles became prominent, while the remainder of the body seemed to be wasting. Examination revealed that the thyroid was palpably enlarged, and the spleen was just below the costal margin; the gastrocnemius muscles were hypertrophied, the patellar reflexes were diminished and the other reflexes absent. Amino-acetic acid therapy, 24 Gm. daily, for six months has not altered the condition.

CASE 24.—A. C., a boy aged 11 years, at the age of 3 years complained of pains in the legs, the muscles of which were prominent. About one year later he had what was said to be "intestinal flu," with diarrhea for two weeks. After this he began to walk on his toes and fell repeatedly. Since the age of 5 years the calf muscles seemed to grow smaller. At 7 years he was unable to raise his

arms, and at 10 years he became bedridden. A few weeks before his admission to the clinic he began to have "choking spells." Biopsy of muscle tissue showed atrophic changes. He was given extract of adrenal cortex intramuscularly and experienced paresthesias in the leg muscles, but no objective improvement was noted. After two years without special therapy, he was given 16 Gm. of amino-acetic acid daily. Gain in weight and decrease in fatigability resulted, and at the time of writing, eight months later, the condition seems arrested.

Case 25.—D. K., a boy aged 10 years, weighed 12 pounds (5,443 Gm.) at birth. At 4 years a waddling gait developed, and he began to fall. He became nervous and irritable. Examination showed prominent calves, wasted thigh muscles, left dorsal scoliosis, lumbar lordosis and diminished deep reflexes. He was given from 15 to 45 drops of solution of epinephrine hydrochloride and 30 grains (1.94 Gm.) of calcium lactate daily for six months, with no striking improvement.

Case 26.—T. W., a boy aged 14 years, had a family history of the grandfather on the mother's side having had a "muscular condition" and the mother chorea as a child. A brother 7 years old had a condition similar to that of the patient. At the age of 5 years the patient began to complain of pain in the calves on exertion, which was relieved by rest. His gait became peculiar, and falls were frequent. The calves were noted to be prominent. At 12 years of age he had a tonsillectomy, because of "difficulty in swallowing." The thighs were wasted, and the reflexes were greatly diminished. There was bilateral equinovarus. Ventricular extrasystoles were prominent. Twelve intramuscular injections of 2 cc. of extract of adrenal cortex gave subjective improvement temporarily. The condition progressed and he was given 100 Gm. of gelatin daily, but with no objective changes.

Case 27.—P. C., a girl aged 4 months, had muscular weakness at 2 months and had never held her head up. The head was rather large; there was marked flaccidity of the lower extremities, and all the reflexes were absent. No bony changes were shown on roentgenographic examination. She died of pneumonia two months after her discharge from the hospital.

Case 28.—D. S., a boy aged 16 months, was brought to the hospital because of weakness of the legs of ten months' duration and weakness of the arms of four months' duration. He had never stood up or walked. He showed marked flaccidity of the lower extremities but no apparent atrophy; the deep reflexes were diminished. Nerve and muscle excitability was diminished, but no reaction of degeneration was noted. His mental age was 17 months. Roentgenograms of the bones showed normal structure. Biopsy of muscle tissue showed atrophic changes. He was given gelatin, 100 Gm. daily, and then amino-acetic acid, 12 Gm. daily, but after six months the condition seems to be slowly progressing.

Case 29.—P. C., a girl aged 4½ years, had never sat up or walked. The lower extremities were weak from birth. Examination showed generalized muscular flaccidity, carious upper molar teeth, a "funnel" chest, flaring of the lower costal margin, "pot belly" and absence of the deep reflexes, except the patellar, which were diminished. No reaction of degeneration was noted. Administration of 5 Gm. of amino-acetic acid daily for seven months produced no change in the condition.

Case 30.—J. T., a girl aged 7 months, had never made any effort to move the lower extremities. Since the age of 4 months the upper extremities seemed weak. A sister died of the same condition at 1 year of age. The infant was hypotonic; the fontanels were closed; the abdomen was protuberant, and the reflexes were

absent. Tests of the spinal fluid gave normal results. Encephalograms showed marked cerebral aplasia. The patient died of an infection of the respiratory tract, at 18 months of age.

CASE 31.—O. D., a boy aged 12 years, had a sudden onset of the condition at 8 years of age. The right side of the face began to twitch, and the speech became slurred. His head fell forward, and he became unable to raise his arms. He was bedridden at 10 years of age. He showed generalized wasting, fibrillary twitchings of the muscles of the chin and shoulder girdle and lateral nystagmus. The deep reflexes of the upper extremities were absent, and atrophy of the muscles of the shoulder girdle was marked. There was a bilateral wrist drop, but no sensory changes or reaction of degeneration could be demonstrated. The electrocardiogram showed ventricular extrasystoles. The chloride content of the blood was reduced, and there was an abnormal salt tolerance curve. No free hydrochloric acid was found in the gastric contents on three occasions. There was no improvement after one month of treatment with 2 ounces (56.7 Gm.) of raw liver daily, a diet rich in salt and dilute hydrochloric acid. The patient died four months later, of what was diagnosed by the family physician as paralysis of the diaphragm and cardiac failure.

CASE 32.—A. D., a boy aged 7 years, whose mother had a peculiar gait, did not hold up his head till 7 months of age. He walked at 18 months, but with a waddling gait, and had frequent falls. He became bedridden one year before his admission to the hospital. Examination showed a tall, thin lad, who had a guttural speech, wasted proximal muscles of the extremities, prominent calf muscles, absence of knee jerks, an undescended right testis and lumbar lordosis. The sella turcica was small. The mental age was 4 years and 8 months. There was disturbance in the salt tolerance. Treatment with a 1 per cent solution of pilocarpine hydrochloride and 0.2 cc. of a 1 : 1,000 solution of epinephrine every other day for eight months produced temporary subjective improvement, but the course of the disease has been slowly progressive. The patient has received 12 Gm. of amino-acetic acid daily for eight months, with definite subjective improvement and no progression of the condition.

CASE 33.—H. S., a boy aged 10¾ years, had not walked well since he was 16 months of age. Progressive muscular weakness and wasting developed, so that he had had to use a wheel-chair since the age of 5 years. Examination showed frontal bossing, beading and flaring of the ribs, right dorsal scoliosis, with elevation of the right scapula, fibrillary twitchings of the pectoral and intercostal muscles, and abolishment of all the deep reflexes. Roentgenograms showed the long bones to be as thin as pipe-stems. Biopsy of muscle tissue showed small fibers, some of which were swollen, with splitting, vacuolation and infiltration with fat. Administration of 5 Gm. of amino-acetic acid daily for six months produced lessened fatigability, increased appetite and gain in weight. The condition seems to be arrested at present.

CASE 34.—H. G., a boy aged 15 years, had had weakness of the legs since the age of 15 months. There was some improvement, but at 5 years of age, after an attack of pertussis, he grew progressively worse. He was of small stature and was mentally deficient; he had lateral nystagmus, paresis and atrophy of the ulnar and hypothenar muscle groups, as well as of the muscles of the shoulder girdle and the peroneal and extensor muscles of the lower extremities and bilateral equinovarus and clawfoot. There were no fibrillations or sensory or electrical changes. The spinal fluid was normal. The course of the illness was not traced.

Case 35.—E. S., a girl aged 6 years, had a brother and sister who had had a condition similar to hers and had died of infections of the respiratory tract, at the age of 3½ and 7 years, respectively. The patient's development was normal until she was 14 months of age, when she began to stand but made no attempt to walk. Examination showed a large head, an expressionless face, generalized muscular flaccidity but no atrophy and absence of reflexes. Examination of the spinal fluid and roentgenograms of the skeleton gave normal findings. Biopsy of the gastrocnemius muscle showed preponderance of small fibers, an increased number of sarcolemmic nuclei, a diminished number of cross-striations and an increased amount of perimuscular fat. The patient has received 12 Gm. of amino-acetic acid daily for fifteen months, but, after early subjective improvement, the course seems to have been progressive.

Case 36.—B. W., a girl aged 11½ years, whose mother was twice married, had a sister and brother with a condition similar to hers. The brother died after an attack of pertussis, at the age of 5 years. The only pregnancy from the second marriage resulted in an infant born prematurely at six months who died shortly after birth. The patient's condition was noted at the age of 6 months, when her head tended to fall backward. Her face was expressionless; she had always tired easily and had been rather inactive. Scoliosis developed two years prior to examination, and the patient for the past six months had had difficulty in climbing stairs. She showed a myopathic facies, with tapir mouth; the head was extended; the scapulae were winged, with elevation of the right shoulder; the pigment of the skin was increased, and there were right dorsal scoliosis, lumbar lordosis, a split first heart sound and extrasystoles. Wasting of the muscles of the shoulder girdle and facial weakness, with dysarthria, were prominent features. The intelligence quotient was 131. Roentgenograms of the skeleton revealed normal structure. Biopsy of muscle tissue showed characteristic changes. The patient was given eleven injections of 1 cc. of solution of anterior pituitary, without any effect on the excretion of creatine and creatinine. Pyuria developed, and pyelograms showed a right hydro-ureter and hydronephrosis. Daily administration of 100 Gm. of gelatin for six weeks and then 12 Gm. of amino-acetic acid for several weeks caused early subjective improvement. The patient began to have dyspnea on exertion, however, and difficulty in swallowing and restlessness developed. Death occurred suddenly, of cardiac and respiratory failure.

Technical and Occasional Notes

GRADUATED JUGULAR COMPRESSION WITH MANOMETRIC TRACINGS OF SPINAL FLUID PRESSURE

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In an earlier communication a method was described for obtaining graduated jugular compression in performing the Queckenstedt test for spinal subarachnoid block.[1] An ordinary blood pressure cuff was wrapped about the neck, with an attached mercury manometer. This provided accurately measured jugular compression and allowed a graded series of pressures to be used in the test for spinal subarachnoid block. It was pointed out that such a method assisted greatly in standardizing the test so that observations by different workers or by the same worker at different times could be correlated.

During the past three years all tests for spinal subarachnoid block carried out at the Montreal Neurological Institute have been made with this method of producing jugular compression. It has been the opinion of the staff that the results have been much more uniform and that partial blocks have been more accurately determined than by previous procedures.

The next step was to make kymographic tracings of changes in pressure during the test. They record automatically the time, degree and duration of jugular compression and the responses of the cerebrospinal fluid pressure. By studying such tracings certain conclusions have already been reached. We report the recording device used at present and submit some observations that have seemed justified so far.

RECORDING MANOMETERS

These are preferable to recording tambours as the readings are constant and the excursion in all positions is directly proportional to the change in pressure. The manometers are made with arms of unequal diameter, allowing a choice in sensitivity. When the proximal arm is wide and the distal arm carrying the float and needle is narrow, a maximum excursion is obtained on the tracing paper. Mercury is the most satisfactory fluid, since the manometers are small and easily portable. The model now in use is shown in figure 1. The proximal arm is of 6 mm. bore tubing and the distal arm of 2 mm. bore tubing. These measurements are only approximate. An applied pressure of 100 mm. of water should give a

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1. Grant, W. T., and Cone, W. V.: Graduated Jugular Compression in the Lumbar Manometric Test for Spinal Subarachnoid Block, Arch. Neurol. & Psychiat. **32**:1194-1201 (Dec.) 1934.

rise in the distal arm of 7.2 mm. of mercury. Actually, on calibrating the instrument, the value was found to be a 6.5 mm. excursion on the tracing paper for each hundred millimeters of water pressure applied. By limiting as much as possible the total mass of mercury, the sensitivity is improved, and the cardiac oscillations usually register on the tracing. The float is a small glass bulb blown on the end of a capillary tube. The pen is a small celluloid cone having a minute hole at its apex. It retains the marking ink by surface tension and adheres to the tracing paper in the same way. To economize in space, the manometer for

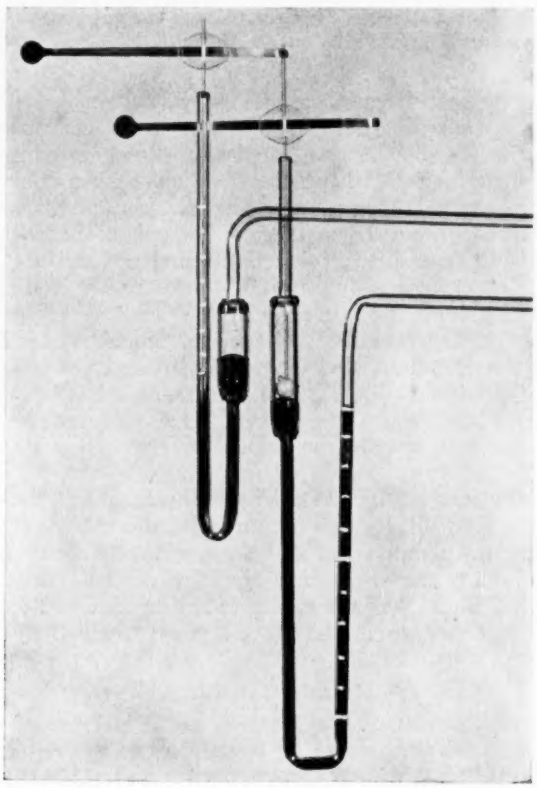

Fig. 1.—Close view of the recording manometers now in use. The manometer on the left is connected with the lumbar puncture needle, and the one on the right, with the cuff about the patient's neck. The two manometers have been separated for the photograph.

recording pressures in the cuff about the neck is made with the float in the wide arm, and the pressure is applied to the narrow arm. The manometers, timer and kymograph are shown in figure 2. The spinal fluid manometer is connected with the lumbar puncture needle by small bore, thick-walled rubber tubing, filled with air. Figure 3 shows a manometric test in progress.

By introducing a time marker, the rate of change in pressure can be worked out much more accurately than by visual readings. As more of the unknown

factors are controlled, exact calculations will become much more significant, and in step with this faster speeds of the drum can be used to reduce the experimental error.

In the tracing it is easy to detect obstruction of the spinal fluid flow caused by the presence of a nerve root over the end of the lumbar puncture needle. Since

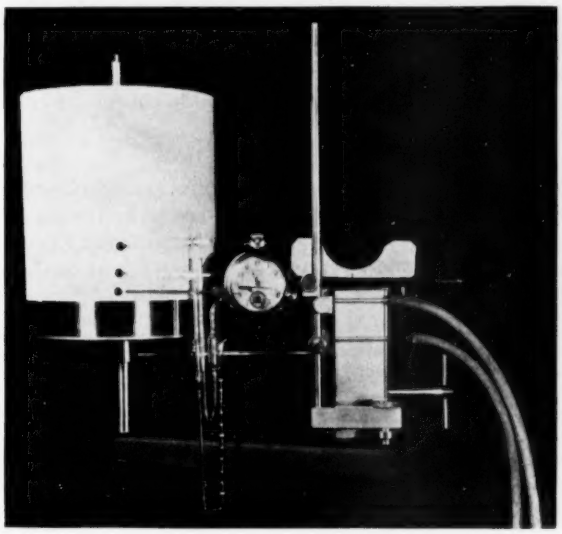

Fig. 2.—Photograph of the manometers mounted for use. The upper needle traces the changes in the spinal fluid pressure; the needle in the center, the changes in cuff pressure, and the lower needle, the time in seconds.

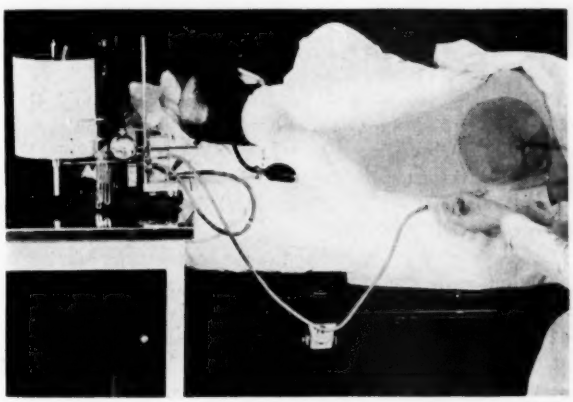

Fig. 3.—Photograph taken during the making of a manometric tracing. The manometers on the left are connected with the blood pressure cuff about the neck and with the lumbar puncture needle, respectively. The nurse has lowered her left hand for the photograph. The tube that leads from the lumbar puncture needle to the manometer is held horizontally during the test.

such a block always occurs suddenly and has a valvelike action, the curve is angulated, and the further rise either is checked or assumes a slower rate.

Occasionally a delayed fall in the spinal fluid pressure is attributable to incomplete relaxation or slight straining by the patient. This too becomes evident as a change in the regular outline of the curve.

The effects of coughing and straining are of the greatest value in patients with complete or partial block. Naturally, the responses vary with the degree of effort expended by the patient. By just filling the cuff without appreciably compressing the neck, the pressure in the cuff is raised during coughing and straining, and an index is obtained of the force with which the patient carries out this part of the test.

ANALYSIS OF TRACINGS

In analyzing the tracings we measure: (1) the lag in rise of the cerebrospinal fluid pressure after application of the cuff pressure; (2) the initial rate of rise; (3) the maximum rate of rise; (4) the amount of rise; (5) the time taken by the cerebrospinal fluid pressure to reach a position of rest; (6) the maximum rate of fall, and (7) the time taken by the cerebrospinal fluid pressure to return

Readings Made in an Analysis of the Tracing Shown in Figure 4 *

	Rise of Cerebrospinal Fluid Pressure					Fall of Cerebrospinal Fluid Pressure	
Cuff Pressure, Mm. of Mercury	Lag, Sec.	Amount, Mm. of Water	Initial Rate, Mm. of Water per Sec.	Maximum Rate, Mm. of Water per Sec.	Time, Sec.	Maximum Rate, Mm. of Water per Sec.	Time, Sec.
10	1.5	30	10	10	4	5	4
20	1.25	52	13	25	5	15	6.5
40	1.25	180	42	52	6.5	32	7.5
60	1.25	355	50	60	9	70	9
80	2.0	456	56	65	11	97	10.5
100	1.3	635	62	73	13	108	15
3 coughs	0	430		800		400	5
Straining	0	600		455	2	263	4

* These values are plotted in figure 5.

to a resting level. This is worked out for each curve, and the results are plotted on a graph. In the graph the ordinates represent the consecutive cuff pressures employed, and the abscissas, the particular cerebrospinal fluid pressure. In general the lag in the response of the cerebrospinal fluid pressure after the cuff pressure has begun to rise is less than three and five-tenths seconds, and in many patients under one second. In some cases only it is shorter when the higher cuff pressures are employed. The amount of rise normally varies in an almost straight line relation with the cuff pressure. To afford a better idea of the type of analysis that is being carried out, a tracing is shown in figure 4, with the values recorded in table 1 and the graphs for the plotted values in figure 5.

The patient from whom the tracings in figure 3 were made had had three verified neurofibromas removed from the lower part of the cervical region four years before, one of which was intradural and extramedullary. He was free from symptoms when the tracing was made. However, analysis showed that the maximum rate of rise diminished relatively at the higher cuff pressures, although the maximum rate of fall did not correspond. It is possible that other neurofibromas, too small to produce symptoms but large enough to impede the flow of spinal fluid during the test, were present.

Partial block is suggested when the responses are slow. Partial block of a different type is one in which the responses are poor at the lower cuff pressures but are of normal height at the higher cuff pressures.

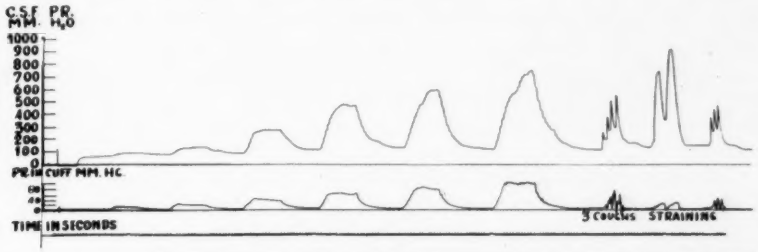

Fig. 4.—Manometric tracing obtained from a patient with von Recklinghausen's disease, mentioned in the text. The responses are adequate, but the rapidity of the rise in the cerebrospinal fluid pressure does not increase progressively as does the rapidity of the fall. The readings from the tracing are plotted on the graphs shown in figure 5. The cardiac oscillations are visible, as well as the larger secondary waves, referred to in the text.

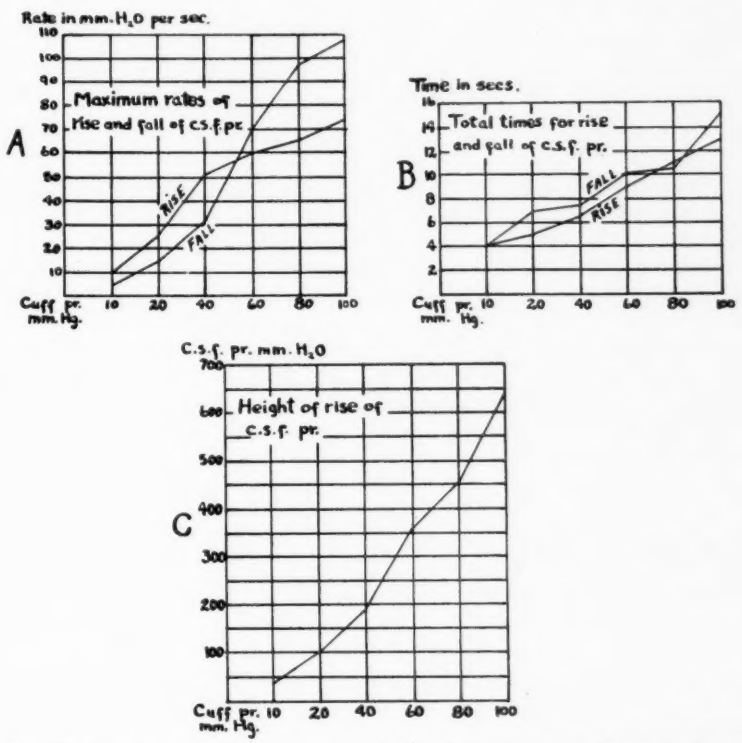

Fig. 5.—Graphs plotted from an analysis of the tracing shown in figure 4. *A* shows a comparison of the maximum rates of rise and fall of the spinal fluid pressure; *B*, the time expressed in seconds required for complete rise and fall of the spinal fluid pressure, and *C*, the height of rise of the spinal fluid pressure at the different grades of jugular compression.

It is not the height of rise that matters but the rate of rise and the lag between the time of application of cuff pressure and the beginning of the spinal fluid response. An even better index than the rate of rise is the time taken to attain a position of rest. This measures the intracranial pressure at any degree of jugular compression. Persons with muscular necks show a much smaller rise in intracranial pressure when the usual cuff pressures are employed.

Most of the tracings show a double wave in the rise of cerebrospinal fluid pressure. This is demonstrated in figure 4. It may represent first the dilatation of surface vessels and later the expansion of the brain due to generalized congestion.

Cardiac pulsations, of course, are stronger at higher intracranial pressures. In cases of complete or partial block the cardiac pulsations should likewise be transmitted less completely.

We have found that comparative responses to coughing and straining in cases in which there is partial or complete block may be used to determine the level of block. When the intra-abdominal or intrathoracic pressure is sufficiently raised the venous drainage from the vertebral canal is impeded. This results in an increase in intraspinal pressure.

While the patient is straining the maximum pressure is exerted on the abdomen, whereas during coughing it is concentrated in the thorax. Hence, in the case of a tumor high in the spinal cord response will be good to both coughing and straining. If the tumor is situated lower the response to coughing will be more and more impeded, while the response to straining is little impaired. Finally, in cases of block in the lower portion of the lumbar or in the sacral region, the response to straining too is less or is absent.

COMMENT

The automatic recording now in use for the determination of spinal subarachnoid block has improved the test and, in our experience, has made the results more dependable. More accurate calculations of the rate of rise and fall of the spinal fluid pressure are possible. Comparison of curves obtained in one case with those in another is greatly facilitated.

As more data are collected and minor variations of response become more significant, other factors will be controlled. Certainly, instantaneous inflation of the cuff about the neck to the desired pressure will be helpful, and measurement of the force used in straining and coughing may be justified.

It is of primary importance that a lumbar puncture needle of constant size be used if the manometric tracings are to be in any way comparable. The rate of response obtained in experimental tracings made with needles of different bore is found to vary with the size of the needle. In all our manometric work we have used a needle of 18 gage.

SUMMARY

A method is described by which jugular compression and the resulting spinal fluid pressures are automatically and simultaneously recorded and timed on a kymograph.

Some advantages of such tracings are illustrated.

The plan of analyzing the tracings is outlined.

Case Reports

SICKLE CELL ANEMIA AS A CAUSE OF CEREBRAL VASCULAR DISEASE

R. H. KAMPMEIER, M.D., NASHVILLE, TENN.

Sickle cell anemia is not generally known to be a possible cause of cerebral vascular accident. Recently, I had experience with such a combination of symptoms occurring in a patient whom I observed on his fifth admission to the Charity Hospital because of neurologic symptoms. Although a different diagnosis had been made on each admission, it seems that a careful analysis of this case justifies the conclusion that sickle cell anemia was the cause of the clinical picture.

A search of the literature revealed three cases in which similar manifestations occurred. However, in the reports of these cases there is little, if any, discussion of the relationship of symptoms and signs originating in the central nervous system to the pathologic and clinical aspects of sickle cell anemia. Therefore, this report of a fourth case is given, with an explanation of the probable cause of events in the production of the clinical picture. Cook [1] published the first account of neurologic symptoms in the presence of sickle cell anemia. His case was that of a Negro boy aged 7 years who had suffered sudden loss of consciousness and in whom evidence of a subarachnoid hemorrhage associated with cerebral softening was noted at necropsy. Cook apparently considered the conditions coincidental. The second report is that of Arena,[2] who reported the symptoms of cramping abdominal pain, headache, vertigo, stupor and right hemiplegia in a Negro boy aged 6 years. Bloody spinal fluid was present. A footnote to this report calls attention to a second patient that Arena had seen. He cited personal communications from Sydenstricker and Cooley covering three more cases but gave no details. Arena merely raised the question whether thrombosis of cerebral vessels may not take place, since it is known that thrombosis occurs elsewhere in sickle cell anemia.

REPORT OF A CASE

A. St. M., a Negro boy aged 10 years, was first admitted to the Charity Hospital on June 29, 1932, in a stuporous condition. The history indicated that three days before admission there had developed vomiting and high fever. Five convulsive seizures occurred in the twenty-four hours preceding admission.

From the Departments of Medicine, Louisiana State University Medical Center and the Charity Hospital, New Orleans, La.

1. Cook, W. C.: A Case of Sickle Cell Anemia with Associated Subarachnoid Hemorrhage, J. Med. **11**:541 (Dec.) 1930.

2. Arena, J. M.: Vascular Accident and Hemiplegia in a Patient with Sickle Cell Anemia, Am. J. Dis. Child. **49**:722 (March) 1935.

Examination at this time gave negative results except for the following findings: the boy was poorly developed and in stupor; the pupils were dilated and did not respond to light; there was no nuchal rigidity; the temperature was 103 F., the pulse rate 120 and the respiratory rate 28.

Laboratory studies of the spinal fluid were made on three occasions. The pressure was consistently normal; the white cells numbered less than 10 per cubic millimeter; the globulin and the Wassermann reaction were negative on each occasion, and the sugar content was 61.5 mg. per hundred cubic centimeters on one examination. Two Wassermann tests of the blood were negative; the nonprotein nitrogen content of the blood was 44 mg., and the sugar content was 90 mg., per hundred cubic centimeters. An agglutination test for the typhoid group of organisms was negative. Urinalysis repeatedly gave negative results. A cell count made several days after admission showed 24,300 white cells, 85 per cent of which were neutrophils and 15 per cent lymphocytes. Two weeks later the count showed 10,300 white cells, 67 per cent of which were neutrophils, 32 per cent lymphocytes and 1 per cent eosinophils.

A roentgenologic study of the skull two days after admission showed only premature synostosis of the coronal sutures. The lungs were clear as seen roentgenologically.

The eyegrounds were found to be normal by the ophthalmologist. A consulting neurologist offered the diagnosis of "acute encephalitis (mesencephalic)." He found no localizing neurologic signs. Sodium iodide was given intravenously. By the tenth day the patient began to talk and take food without the nasal tube. On the twenty-first day he again became stuporous, and the temperature rose to 105 F. Improvement then quickly followed. For the first twenty days the temperature fluctuated from 100 to 104 F.; it was 99 F. for seven days before the patient's discharge.

The patient was discharged one month after admission. The diagnosis was epidemic encephalitis.

Second Admission.—This was on July 20, 1933. The patient, in stupor, was admitted to a neurologic ward. The history, as obtained from the mother, indicated that five days before admission the boy had complained of violent cramping pains in the epigastrium; he had been nauseated, had vomited and gradually had become stuporous. Two days before admission he had a convulsion, during which he had bitten his tongue.

When examined the patient was groaning and twisting about in bed; otherwise, except for the stupor, there were no findings of note.

Two examinations of the spinal fluid and Wassermann tests of the blood gave negative results as on the first admission. A white blood cell count was not made.

By the third day the patient was clear mentally. The temperature ranged from 99 to 100 F. He was discharged in one week. The diagnosis was idiopathic epilepsy.

Third Admission.—The patient was admitted a third time on June 25, 1934. Six days before admisison he had begun to complain of pain in the upper portion of the abdomen; during attacks of pain he would grasp the scrotum. Pain persisted to the date of admission and was accompanied by urinary frequency. On the night before admission the boy began to have "weak spells" characterized by spasms about the mouth, falling back in bed and "rolling" of the eyes. There had been no general convulsions or loss of consciousness. Vomiting had occurred once. Fever had apparently been present since the onset of the attack. The patient had been perfectly well since the last admission, one year previously.

Examination showed that the patient was semistuporous and restless. The pupils were equal. The blood pressure was 92 systolic and 50 diastolic. The abdomen was relaxed. No neurologic signs were present.

The spinal fluid was normal, as before. A Wassermann test of the blood was negative. The total nonprotein nitrogen content of the blood was 63 mg. per hundred cubic centimeters; the creatinine content, 2 mg., and the sugar content, 64 mg. Agglutination tests for organisms of the typhoid and melitensis groups were negative. The urine showed nothing of interest on several occasions. A differential cell count showed 21,400 leukocytes, 81 per cent of which were neutrophils, 17 per cent lymphocytes and 2 per cent monocytes. Examination of the stool disclosed no parasites.

Roentgen study of the skull revealed no abnormalities.

During the first eight days in the hospital the patient was restless; he exhibited alternating periods of semistupor; he frequently complained of abdominal pain, though the abdomen was always normal on examination. Ten days after admission he was much better, and a dextrose tolerance test gave the following results: During fasting the sugar content of the blood was too low to read; thirty minutes after administration of dextrose it was 63 mg. per hundred cubic centimeters; sixty minutes after administration of dextrose it was too low to read, and ninety minutes after administration of dextrose it was 55 mg. per hundred cubic centimeters. The temperature on admission was 102 F.; after several days it ranged from 99 to 100 F.

The patient was discharged eighteen days after admission; the diagnosis was hypoglycemia.

Fourth Admission.—The boy was readmitted on July 26, 1934. He had been well since the previous discharge from the hospital until three days before admission, when he again began to have abdominal pain. Salts did not relieve the pain, which was colicky, lasted a few minutes at a time and often awakened the patient from sleep.

Examination gave negative results except for a soft systolic blow at the apex of the heart. The abdominal and neurologic examination revealed nothing of significance.

A Wassermann test of the blood was negative. During fasting the sugar content of the blood was 83 mg. per hundred cubic centimeters. The urine was normal. The blood contained 40 per cent hemoglobin, 3,060,000 erythrocytes and 12,250 leukocytes. A smear revealed 70 per cent neutrophils, 29 per cent lymphocytes, 1 per cent eosinophils and an occasional nucleated red cell. This study led to an examination for sickling of the red cells. Such a study was made by an experienced observer, who found 40 per cent sickling in eighteen hours. A reticulocyte count showed 10 per cent reticulated cells.

The abdominal pain gradually disappeared. The temperature ranged from 99 to 101 F. After three weeks the boy was discharged. The diagnosis was latent sickle cell anemia.

Fifth Admission.—The patient, then aged 13 years, was again admitted on June 12, 1935, and it was at this time that I first saw him.

He had been entirely free from symptoms since he was discharged from the hospital ten months before. Several days before this admission he had again begun to have colicky abdominal pain, and on the day before admission he had had several convulsions, followed by coma.

When examined the patient was in coma. Except for the neurologic findings there was nothing of note. The pupils reacted sluggishly to light. There were

paralysis of the right side of the face and ptosis of the right eyelid, which were obvious when the patient cried out, as he consistently did on being moved or on movement of an extremity. Spastic paralysis of the right upper and lower extremities was present. The tendon reflexes were markedly exaggerated, and a positive Babinski reflex was present on the right. A Kernig reaction was apparent bilaterally. Ankle clonus was present on the right side.

A spinal puncture was made on the second day after admission. The fluid was uniformly bloody. Four and six days after the first puncture the fluid was again examined. On these two occasions also the fluid was frankly bloody, showing 400 red cells and about 50 white cells per cubic millimeter and a trace of globulin. The pressure varied from 20 to 28 mm. of mercury at these times. No difficulty was encountered in making the punctures with the patient lying on his side. Four days after the third tap fluid was again obtained. This time it presented a uniform yellow color; the pressure was 12 mm.

The urea nitrogen content of the blood was 76 mg., the creatinine content 21 mg. and the sugar content 76 mg. per hundred cubic centimeters. The icterus index several days after admission was 15.

Sickling of the red cells appeared within four hours. The hemoglobin content was 7.5 Gm.; the red cells numbered 3,070,000, and the white cells, 13,050. Anisocytosis, poikilocytosis and polychromatophilia were present. The differential count showed 70 per cent segmented and 4 per cent stab neutrophils, 8 per cent eosinophils, 0.5 per cent basophils, 12 per cent lymphocytes and 5.5 per cent monocytes. The amount of urobilinogen two weeks after admission was within normal limits, at which time the icterus index had dropped to 10.

Roentgenologic examination of the skull showed no abnormalities.

The temperature was from 99 to 100 F. rectally throughout the stay in the hospital. The semicomatose and restless condition persisted without improvement for two weeks. Tube feeding was used. Five days after admission the weakness of the facial muscles had improved. Three weeks after entry the stupor had definitely disappeared, and the boy was looking at pictures in the newspaper. He began to speak a few words to his mother, though speech was halting. By the fourth week the patient could move the right lower extremity fairly well and was speaking somewhat better. Signs of spasticity were still present.

The patient was discharged five weeks after admission to the hospital.

He has been examined at intervals. The last examination, in November 1935, showed a residual spasticity on the right side.

The patient had five admissions to the Charity Hospital in three years. Between the times of recurrence of symptoms he had been well, and his work in school was above the average. On these admissions the patient was studied and examined at one time or another by three internists and four neurologists.

The symptoms present on each admission were abdominal pain and fever. Generalized convulsions were present on three entries and twitching of the face on a fourth admission. Stupor or coma was present each time, except on the fourth examination, which was the only time when neurologic symptoms were not present and was the time when the diagnosis of sickle cell anemia was first considered, because of fever, abdominal pain and leukocytosis. At previous admissions the neurologic symptoms had clouded the picture. Results of the dextrose tolerance test made on the third admission may be disre-

garded, since the inconclusive findings probably resulted from some factor leading to incomplete absorption. Single determinations of the sugar content of the blood during fasting on four of the admissions showed reading within normal limits, the value on two occasions being at least 90 mg. per hundred cubic centimeters during the period of stupor.

The diagnoses on the charts are of interest because of the variety. On the successive admissions they were, respectively, epidemic encephalitis, idiopathic epilepsy, hypoglycemia, latent sickle cell anemia (on the admission at which no symptoms were present referable to the nervous system) and, finally, on the fifth admission, cerebral hemorrhage with hemiplegia due to sickle cell anemia. On the last admission a neurologist suggested tumor of the brain.

COMMENT

Sickle cell anemia is found practically exclusively in Negroes or in persons with Negro blood. About 7 per cent of all Negroes are supposed to show latent sickling or sicklemia. Active sickling, that is, the clinical picture of sickle cell anemia, is found more often in males than in females, and more often in young patients, though at no age are patients immune from exacerbations.

The immediate etiologic factors leading to attacks are not well known, though it is believed that acute infection may be the precipitating factor. Characteristically, an attack of sickle cell anemia shows one or more of the following symptoms: weakness, abdominal pain, nausea, vomiting, headaches, dizziness, night sweats, chills, fever, dyspnea, palpitation, pains in the joints and muscles and ulcers of the legs. Physical findings consist of generalized lymphadenopathy, icteric scleras, cardiac enlargement, a systolic murmur at the apex, edema, hypotension, enlargement of the liver and spleen, jaundice and swelling of the joints. The urine may show albumin and casts. The icterus index is increased. Leukocytosis, the number of leukocytes varying from 10,000 to 60,000, is usually present; the differential cell count is usually not remarkable, though nucleated red cells are often found in the smear. As a result of a hemolytic process in the active stage of the disease, secondary anemia is usually present; the red cells show variation in size and shape and stippling. Sickle-shaped cells may be present or appear in a sealed drop preparation within twenty-four hours.

This is not the place to discuss the pathology of sickle cell anemia in detail. A number of papers in the literature are devoted to necropsy observations and discussion of the pathology. However, certain pathologic features must be mentioned in order to establish a basis for my thesis that symptoms and signs referable to the central nervous system may be satisfactorily accounted for by this disease.

Though the spleen, as removed at operation early in the course of the disease, is enlarged, deep purple and turgid, its condition at necropsy after longer duration of the disease is markedly different. Then it is found to be atrophic, often very small, and to present a rough surface. The capsule and trabeculae are reported to be greatly thickened. Iron pigment is present owing to the long-standing hemolytic process. The smaller splenic vessels show obliteration or thrombosis, this change

probably accounting for the atrophic state of the spleen and the numerous scars due to infarcts. Ulcers of the leg are of the punched-out type and show perivascular infiltration with mononuclear cells. The myocardium may show patchy fatty metamorphosis. The kidneys, according to several authors, often have an irregular scarred surface, microscopically showing capsular and radial scarring and often glomerular fibrosis. Steinberg,[3] in reviewing the sixteen necropsies on patients with sickle cell anemia reported in the literature, said that five patients had either pulmonary tuberculosis or bronchopneumonia, which probably overshadowed any other pathologic changes in the lungs which might have been present. He stated further that four others were reported as showing congestion of capillaries and larger vessels. Steinberg himself described the pathologic changes in the lungs in his case as consisting of fresh or organized thrombi in the small and medium-sized pulmonary vessels, some being canalized. There were old and fresh infarcts. Wollstein and Kreidel [4] described a wedge-shaped area of organized pneumonia observed in one of their patients which they attributed to previous infection of the respiratory tract.

I have chosen to call attention to the reported pathologic lesions which are on a basis of vascular disease, namely, thrombosis.

CONCLUSIONS

If thrombosis occurs in vessels in the various organs—spleen, lungs, kidneys, etc.—it is within the realm of probability that it also occurs in the vessels of the brain and meninges. Cook's case indicates this probability. Cerebral softening had occurred, indicating not a simple subarachnoid hemorrhage, as this author supposed, but involvement of the cortex by infarction. Softening would probably not have occurred with simple subarachnoid bleeding. In my case, on previous admissions small vessels or capillaries may have been thrombosed without bleeding into the subarachnoid space. I believe that at the time of the last admission thrombosis with hemorrhagic infarct occurred, being associated with bleeding into the subarachnoid space. This would explain the hemiplegia, including the paralysis of the right side of the face, indicating cortical involvement on the left side. Repeated evidence of blood in the spinal fluid could also be accounted for on this basis.

SUMMARY

The case of a Negro boy suffering from sickle anemia is reported. There were repeated attacks of disturbance referable to the central nervous system, in the last of which there was hemiplegia. Pathologic changes characteristic of sickle cell anemia permit the diagnosis of cerebral thrombosis on this basis. This is the fourth case reported in the literature in which similar manifestations occurred. I have attempted to explain the neurologic picture on the basis of known pathologic

3. Steinberg, B.: Sickle Cell Anemia, Arch. Path. **9**:876 (April) 1930.

4. Wollstein, M., and Kreidel, K. U.: Sickle Cell Anemia, Am. J. Dis. Child. **36**:998 (Nov.) 1928.

changes in the disease. Hitherto other authors have considered the relationships to be more or less coincidental.

NOTE.—In a recent paper by Yater and Hansmann [5] there is presented pathologic evidence of vascular disease in the central nervous system. This was in the case of a Negress, aged 38, who presented no neurologic symptoms.

The authors observed at necropsy "some recent diapedesis of the red blood cells into the meninges over the right hemisphere. There was a small area of softening 1 cm. in diameter in the cortex in the left parietal region. The choroid plexus was uniformly shrunken and of ashen color and in places appeared as a white cord. Gross serial sections of the cord revealed small petechiae in the nerve trunks as they emerged from the cord to enter the dorsal root ganglia in the dorsal and lumbar regions." The microscopic observations are also presented.

5. Yater, W. M., and Hansmann, G. H.: Sickle Cell Anemia: A New Cause of Cor Pulmonale; Report of Two Cases with Numerous Disseminated Occlusions of the Small Pulmonary Arteries, Am. J. M. Sc. **191**:474 (April) 1936.

Obituaries

CHARLES HARRISON FRAZIER, M.D.
1870-1936

Charles Harrison Frazier was born in Philadelphia, April 19, 1870. His early education was obtained at the Episcopal Academy, and he entered the University of Pennsylvania, graduating in the class of 1889. After some thought, he entered the medical school of the University of Pennsylvania. On the completion of four years in medicine in 1892 and two years' hospital internships in the Hospital of the University of Pennsylvania and the Episcopal Hospital in Philadelphia, he spent a year or more in Europe studying surgery, surgical pathology and neurology under von Bergmann and Virchow. When he returned to Philadelphia, he received appointments to the surgical service in the Hospital of the University of Pennsylvania and to the teaching staff of the medical school. His ability as a teacher and organizer was promptly recognized by his appointment in 1901 as professor of clinical surgery and dean of the medical school of the University of Pennsylvania.

Dr. Frazier had become interested in neurology during his sojourn in Europe. Philadelphia at this period was the center of a great group of neurologists. Mitchell was active and had inspired Mills, Dercum, Spiller, Burr, Weisenburg, Bond, Strecker and other young men to take full advantage of the clinical and pathologic material available at Blockley and the Philadelphia Orthopaedic Hospital. Working with Spiller, Frazier showed that preganglionic section of the sensory root of the fifth nerve was as permanent a measure for the relief of the pain of major trigeminal neuralgia as avulsion of the ganglion and a much safer surgical procedure. The close cooperation of these two men—Spiller, a great and profound neurologist, and Frazier, an ingenious technician and wise surgeon—was interesting and unique. One complemented the other, Spiller suggesting and outlining the problems and Frazier working out the practical surgical methods necessary for their clinical use. Chordotomy, or section of the anterolateral columns of the spinal cord, for the relief of pain was developed through this association of neurologist and neurosurgeon.

Dr. Frazier was elected to the American Neurological Association in 1905. He was president of the association in 1928-1929. Many papers under his name were read before this group—on tumors of the

brain and spinal cord; the surgical treatment of major trigeminal neuralgia, especially with regard to subtotal section of the sensory root, the ophthalmic branches being thus spared to protect the eye; atypical or minor neuralgias; the morphologic development of the ganglion of Gasser, and section of the anterolateral tracts of the spinal cord for the relief of intractable pain.

Many honors came to Dr. Frazier. He was a member of the College of Physicians and the Academy of Surgery in Philadelphia; a Fellow

CHARLES HARRISON FRAZIER, M.D.
1870-1936

of the American College of Surgeons; a member of the American Surgical Association; a founder member and president in 1922-1923 of the Society of Neurological Surgeons; a member of the Association for Research in Nervous and Mental Disease, of the American Society for the Study of Goiter, and of the Deutsche Akademie der Naturforscher, and an honorary member of the British Neurological Society.

During the World War he was a neurosurgical consultant to the Surgeon General and, with the rank of lieutenant colonel, was in

charge of the neurosurgical service in Base Hospital 11, at Cape May, N. J., and Base Hospital 41, at Fox Hills, Staten Island, N. Y. In 1920 he represented the Surgeon General at the Interallied Surgical Conference in Paris, presenting a paper on injuries of peripheral nerves.

In 1922 he was appointed John Rhea Barton professor of surgery in the University of Pennsylvania School of Medicine and chief of the surgical service at the Hospital of the University of Pennsylvania. His interests were confined to neurosurgical problems and thyroid surgery.

In 1925 he received the degree of Sc.D. from the University of Pennsylvania and in 1934 was elected a trustee of the university.

Dr. Frazier was a great organizer and an indefatigable worker. The present surgical service at the Hospital of the University of Pennsylvania stands as a memorial to his efforts, a service in which the interrelationship between the teaching staff, the students and the clinical material has been worked out to great mutual advantage. He was a pioneer in recognizing the value of surgical research and the need for close cooperation between the preclinical and the clinical departments, with particular emphasis on the physiologic and pathologic basis for every surgical procedure.

His great ability was to think clearly, to strip a problem of its nonessentials and to reach conclusions based on a large clinical experience and hard common sense. Energetic and hard driving, he often seemed abrupt and curt. But those who knew him well, who had the opportunity to see his meticulous technic and unending patience during difficult intracranial operations and who were privileged to share his charming moments of relaxation held him in the deepest affection and esteem.

He died July 26, 1936, in North Haven, Maine. In the last months of his life he suffered intense pain. But his interest in his work never flagged. In spite of great physical distress, he insisted on attending the meetings of the Society of Neurological Surgeons and the American Neurological Association. Never did he complain; never did he lose interest in his work. Until the last he was himself—alert, competent and charming, fighting down his discomforts so gallantly that it was an inspiration to all to see him.

FRANCIS C. GRANT, M.D.

Abstracts from Current Literature

Physiology and Biochemistry

STRENGTH DURATION CURVES OF THE OVEREXCITABLE AND UNDEREXCITABLE NERVE MUSCLE APPARATUS AND SOME CONSEQUENCES BEARING ON THE CLINICAL APPLICATION OF CHRONAXIMETRY. F. H. LEWY, Am. J. M. Sc. **191**:491 (April) 1936.

In view of the fact that Lapicque's experience was confined mostly to normal nerve-muscle apparatus, the problem remained whether chronaxia alone was a suitable index of irritability under pathologic conditions. This study was based on the chronaximetric examinations of 825 lead workers subjected to different degrees of exposure. The theoretical deductions were: (1) Curves for duration of strength of the overexcitable and underexcitable nerve-muscle apparatus are hyperbolas, differing in the degree of curvature, and (2) by means of two independent measurements of the excitation time—one of which may be the chronaxia—and by three simple calculations, one can determine the vertex characteristic. This symbol defines with sufficient exactitude the shape of the hyperbola on which the chronaxia is situated. A method had to be evolved for use as a routine to establish whether or not the stimulated point was really the optimal one, which is a point on the skin by stimulation of which the virtual cathode within the nerve obtained its greatest density. In the first stages of a nerve lesion and in the last stages of degeneration it is usually impossible to obtain a satisfactory approximation of the three values of the vertex characteristic. In the majority of cases the threshold for the cathode was lower than that for the anode. Neither rheobase nor chronaxia alone gives the right impression of irritability. A greater number of the subjects examined were found to be on the borderline between a normal and an abnormal degree. Three formulas are given for calculating the vertex characteristic by help of two independent pairs of measurements, carried out at one and the same point on the muscle.

MICHAELS, Boston.

PLASMA LIPIDS OF NORMAL MEN AT DIFFERENT AGES. IRVINE H. PAGE, ESBEN KIRK, WILLIAM H. LEWIS JR., WILLIAM R. THOMPSON and DONALD D. VAN SLYKE, J. Biol. Chem. **111**:613, 1935.

The objects in this paper were: (1) to ascertain the effect of age, beginning with the third decade, on the lipid content of the plasma of normal men and (2) to ascertain for adult men the normal ranges of the different lipid fractions determined by the gasometric method utilized by Kirk, Page and Van Slyke. A statistical analysis of the results of 390 determinations was made. It showed that variation in age, from 20 to 90, had no determinable influence on either the amount or the composition of the plasma lipids. Evidence was obtained that part of the aminonitrogen and nonaminonitrogen found in the petroleum ether extracts appears to be derived from substances other than the usual phosphatides. These substances have as yet not been identified. Tables are presented giving the mean values and ranges for postabsorptive concentrations of plasma lipids. These include values for free, ester and total cholesterol, total lipids, neutral fats, lipid phosphorus and phosphatides, lipid aminonitrogen and total lipid nitrogen. Normal standards of this character are essential for comparison when analysis suggests that lipid metabolism is abnormal. The wide latitude exhibited in the normal range cautions against acceptance of uncritically analyzed "abnormal" values. Many of the data concerned with lipid metabolism of patients suffering from nervous and mental disease require reanalysis with more rigidly established normal values.

PAGE, New York.

THE COPPER CONTENT OF URINE OF NORMAL CHILDREN. ALAN ROSS and I. M. RABINOWITCH, J. Biol. Chem. **111**:803, 1935.

Copper is a normal constituent of urine, the amounts in adults ranging from a mere trace to 0.4 mg. per liter. In view of the importance generally attached to copper in the metabolism of iron (formation of hemoglobin, etc.) and its widespread and increasing use in diseases of children, it was considered of importance to ascertain the normal urinary excretion of copper in children. In boys from 8 to 17 years of age it varied from 0.04 to 0.52 mg. per liter and from 0.026 to 0.62 mg. a day. It is of interest that the brain also contains rather large amounts of copper. It is especially rich in the fetal brain.

PAGE, New York.

OBSERVATIONS ON CARDIAC ACTIVITY IN THE FETAL RAT. E. L. COREY, J. Exper. Zoöl. **72**:127 (Nov. 5) 1935.

By a delicate suspension method (not described) cardiac tracings were secured from fetuses of 230 rats; these fetuses averaged 31 mm. in crown-rump length and comprised sixty-one litters. Synchronous maternal records were also taken whenever pertinent. Decerebration (thirty-six litters) or light ether anesthesia (twenty litters) was employed to immobilize the mother. This study was an extension of previous work on the fetal heart rate. Of the extrinsic factors, it was found that temperature changes, lactic acid and asphyxia produced irregularity in the fetal heart rate, while sudden changes in maternal blood pressure or administration of alkaline solutions was not effective. Experimental procedures showed that the fetal cardiac nerves, both vagal and sympathetic, functioned. These observations were checked by the use of pilocarpine and atropine. However, no reaction to epinephrine or to stimulation of the adrenal secretion could be demonstrated. Thus it is indicated that nerve influences on the central circulatory mechanism have precedence temporally over humoral agencies. A positive reaction to epinephrine was obtained at the end of the first week of postnatal life.

WYMAN, Boston.

PAIN: THE PERIPHERAL PATHWAY. G. K. STÜRUP and E. A. CARMICHAEL, Brain **58**:216, 1935.

To explain the appreciation of pain in a limb rendered apparently analgesic by a lesion of the plexus or by section of the spinothalamic tracts, it has been suggested that pain impulses may utilize the periarterial plexus or sympathetic chain to gain entrance to the spinal cord. If the hypothesis is true that pain may be carried centripetally by such paths, it should be possible to establish anatomically the presence of fibers passing the whole length of an artery to the periphery of a limb. Experimental histologic investigations by Busch (1927) and anatomic investigations by Coates (1932) favor the view that pain is not likely to be transmitted along the periarterial network from the periphery. These anatomic studies have received confirmation in the work of Woollard and Phillips (1932) and Davis and Pollock (1930). Foerster (1927) and Foerster, Altenburger and Kroll (1929) deduced from a study of pathologic material that the periarterial plexus may carry sensory stimuli from the periphery of a limb and that the sympathetic chain may carry sensory impulses from the legs to enter the cord above the level of a spinal or root lesion.

Using two healthy young men, Stürup and Carmichael made the following investigation: The left ulnar nerve was blocked, and complete sensory loss in the distribution of the ulnar nerve was obtained. The digital artery and nerve on the ulnar side of the base of the fifth digit were then exposed by open dissection. Stimulation of the exposed artery and nerve by a faradic current resulted in no sensation of any character being perceived by the subject. Clamping, pulling and

stretching the artery gave rise to no sensation. The blocking of the ulnar nerve in no way reached the periarterial plexus surrounding the brachial artery, as the artery lay anterior to the elbow joint.

It is not to be assumed from these experiments that sensory fibers and nerve endings on arteries are not to be observed. Pain resulting from experimental puncture of an artery as well as from the placing of hemostatic forceps is well known. The experiments described afford proof only that such sensory fibers travel but a short distance along the artery before they leave it to join a peripheral nerve.

SALL, Philadelphia.

SHIVERING: A CLINICAL STUDY WITH ESPECIAL REFERENCES TO THE AFFERENT AND EFFERENT PATHWAYS. V. UPRUS, G. B. GAYLOR and E. A. CARMICHAEL, Brain **58**:220, 1935.

This study was undertaken to investigate the pathways subserving the afferent and efferent portions of the shivering mechanism involved in alterations in temperature. The trend of the work of previous investigators pointed to the existence of a cephalic center necessary for the production of shivering. In the present investigation two series of studies were undertaken—one on a group of healthy young men and the other on a group of patients presenting evidences of lesions of the nervous system. Both groups were subjected to the same experiments.

The following method was employed: After a period used as a control the legs were immersed up to the tibial tuberosity in warm water until adequate warming took place. They were then immersed immediately in cold water until shivering took place. When shivering had become uncontrollable, the legs were transferred to warm water until shivering ceased. The rectal temperature, obtained by means of a special thermocouple, was recorded during the course of the experiment and was accepted as indicating the temperature of the arterial blood.

In the investigation of normal subjects the constancy of the production of shivering during a phase of rapid fall in the blood temperature suggests that changes in blood temperature may be of significance. Two findings were of constant occurrence: first, the period of latency between the application of the sensory stimulus of cold to the immersed limbs and the onset of shivering and, second, the cessation of shivering near the lowest point on the blood temperature curve, which occurred some time after the legs had been immersed in warm water. The period of latency between immersion in cold water and the commencement of shivering is against the view that the mechanism of shivering is entirely reflex, unless summation of stimuli is invoked to explain the occurrence. The type of shivering produced in these investigations on normal persons ceased after the limbs had been heated for some time but not before there was a definite alteration in the rate of fall of blood temperature or a definite rise. This fact again suggests the possibility that the blood temperature plays an important part in the causation of shivering.

The same experiments were carried out with patients with: complete transverse lesion of the spinal cord, lesions involving the pyramidal tract in the cerebral hemisphere, lesions of the thalamus or the cerebellum and cerebellar pathways and bilateral chordotomy. Shivering was induced in all the patients. A remarkable phenomenon was observed in the patient with a cerebellar lesion: Although shivering occurred, the movements were modified from the clonic to the choreiform type. In a case of unilateral lesion of the cerebellum the temporal relationship of the shivering and the rectal temperature was identical with that in the normal subject, and on the side of the lesion the shivering was of a choreiform type. Thus, it appears that an intact cerebellum is necessary for the production of the clonic movements of shivering. In subjects with a transverse lesion of the cord it was noted that no shivering occurred below the segmental level of the lesion, although reflex activity was present. Shivering of the type seen in normal persons occurred only in muscles innervated from above the segmental level of the lesion. In the subject with bilateral chordotomy the spino-

thalamic tract had been cut on the two sides at the level of the third and the fifth dorsal segment, respectively. There were complete sensory loss up to the level of section and involvement of the pyramidal pathways. In this case shivering was induced in muscles above the segmental level of the lesion. In the other cases of lesions of the nervous system, shivering was induced as in normal subjects.

Thus, shivering is independent of pyramidal, thalamic and cerebellar integrity, although the type of tremor is modified by cerebellar dysfunction. There are left for consideration only the extrapyramidal pathways, such as the tectospinal and the rubrospinal tract. These tracts descend in the spinal cord in areas which would be sectioned by chordotomy. The conclusion is reached that the effective stimulus is a falling blood temperature, which acts directly on a center or a thermosensory mechanism capable of stimulating the shivering center. The descending pathway from the center is shown, by exclusion, to be extrapyramidal, either the tectospinal or the rubrospinal tract.

SALL, Philadelphia.

ON THE REFLEX REGULATION OF THE CEREBRAL BLOOD FLOW AND THE CEREBRAL VASOMOTOR TONE. J. J. BOUCKAERT and C. HEYMANS, J. Physiol. **84**:367 (July 24) 1935.

In previous papers Bouckaert and Heymans showed with several technics that in dogs the carotid sinus reflex does not affect the cerebral vasomotor tone in an active way; indeed, lowering the pressure in the carotid sinus produces a passive increase in the cerebral blood supply, which is due to the reflex increase in the general arterial blood pressure, while, conversely, increasing the pressure in the carotid sinus produces a passive decrease in the cerebral blood flow due to the reflex decrease in the general arterial blood pressure.

In the case of a fall of the carotid blood pressure, the blood is diverted by means of the carotid sinus reflex from the somatic and peripheral cephalic areas to the cerebral circulation, the blood vessels of which do not participate actively in the carotid sinus reflex. The blood flow to the central nervous system thus increases, while, on the other hand, the blood flow to the muscles and skin of the head and to the somatic organs decreases as a result of the reflex vasoconstriction. The cerebral blood supply is thus passively dependent on the general arterial pressure, which is regulated by the carotid sinus and aortic reflexes.

Recently, M. Schneider and D. Schneider confirmed these experimental observations and conclusions concerning the influence of the carotid sinus reflex on the cerebral circulation. They, however, concluded from another series of experiments that the blood pressure also regulates actively the cerebral vasomotor tone by means of a reflex mechanism, the origin of which should be localized not in the carotid sinus but in the middle meningeal artery. According to these authors, lowering or increasing the pressure in the middle meningeal artery puts into action, respectively, reflex vasodilatation and reflex vasoconstriction in the cerebral circulation. These conclusions of Schneider and Schneider were supported also by Gollwitzer-Meier and Eckardt.

In the experiments described in this paper, Bouckaert and Heymans investigated the theory advanced by Schneider and Schneider. They demonstrated that an important branch connects the internal maxillary artery, which is the prolongation of the external carotid artery, with the internal carotid artery and the circulus Willisii. This branch is physiologically important for the cerebral blood supply, since it is sufficient to keep the centers alive and in good condition when the brain is perfused only through the external carotid arteries, all other cerebral arteries being ligated. The authors further demonstrated that the increased flow in the internal carotid artery after clamping the external carotid artery has its origin not in the middle meningeal artery, as propounded by Schneider and Schneider, but in the anastomosis which connects the internal carotid with the external carotid artery. Clamping the internal maxillary artery beyond the middle meningeal artery and before the origin of the anastomotic branch produces the typical change in the peripheral resistance in the internal carotid artery which is observed also after clamping the origin only of the ophthalmic artery giving off the anastomotic

branch. On the other hand, clamping the internal maxillary artery before the origin of the middle meningeal artery after ligating the anastomotic branch does not affect the circulation through the internal carotid artery. The phenomena described by Schneider and Schneider must be explained further by hydrodynamic factors, since they are just as marked in a decerebrate as in a normal animal.

As a consequence of the important direct connections existing in the circulus Willisii between the arteries supplying the nerve centers, a purely hydrodynamic mechanism must also be admitted to explain the increase of blood flow in the internal carotid artery when the external carotid artery is clamped, not on the same but on the opposite side. The same purely hydrodynamic mechanism explains why, in the experiments of Gollwitzer-Meier and Eckardt, the occlusion of several arteries supplying the bulbo-encephalic centers increases the flow in the other arteries to the circulus Willisii.

The experiments of Bouckaert and Heymans support not the existence of vasomotor reflexes which control the vasomotor tone of the brain in relation to changes in blood pressure in the meningeal or cerebral vascular areas but the conclusions of their previous papers concerning the passive changes in the cerebral blood flow due to modifications in the arterial blood pressure and also concerning the mechanism and rôle of the carotid sinus reflex in the regulation of the cerebral blood flow and the cerebral blood pressure. ALPERS, Philadelphia.

BLOOD FLOW IN THE RABBIT'S BRAIN. H. WINTERSTEIN, Arch. f. d. ges. Physiol. **235**:377, 1935.

The rate of the blood flow through the rabbit's brain was measured by inserting Fleisch's differential membrane manometer between the common carotid and the internal carotid artery on one side while the other cerebral arteries were ligated. The average rate was 60 cc. a minute in 100 Gm. of brain. Under normal conditions, however, this value may be higher, for ligation of the cerebral vessels as performed in these experiments is not always quite compensated. Stimulation as well as extirpation of the cervical sympathetic ganglion had no effect on the cerebral blood flow as measured by this method, while both epinephrine and acetylcholine induced a vasodilator effect. The injection of these hormones into the internal carotid artery inhibited the respiration, probably owing to a direct effect on the respiratory center. SPIEGEL, Philadelphia.

INFLUENCE OF CENTRIPETAL PULMONARY VAGUS FIBERS ON THE POSITION AND MOVEMENTS OF THE DIAPHRAGM. J. W. G. TER BRAAK and J. VAN NIEKERK, Arch. f. d. ges. Physiol. **235**:582, 1935.

According to the theory of Hering and Breuer, vagotomy is followed by increased inspiratory contraction of the diaphragm, while Hess assumed that the expiratory relaxation is increased. The present experiments are in agreement with the conception of Hering and Breuer. After bilateral vagotomy the amplitude of the diaphragmatic movements was increased, owing to increased inspiration. If the wall of the thorax was removed so that the movements of the lung and those of the diaphragm were independent of each other, inflation of the lung first stopped the diaphragmatic movements in the expiratory position and then reduced the amplitude of inspiration and increased the frequency of respiration. These effects were abolished by bilateral vagotomy. SPIEGEL, Philadelphia.

Neuropathology

NEUROPATHOLOGIC CHANGES IN EXPERIMENTAL VITAMIN DEFICIENCY. M. C. L. GILDEA and OTHERS, Am. J. Path. **11**:669, 1935.

Seventeen dogs given a diet deficient in vitamin B (Cowgill) showed signs of acute disturbance of the central nervous system and died without treatment with vitamin B concentrates. Only minimal histologic changes were observed in the

central nervous system. Eight dogs which were given a similar diet but in which the acute neurologic signs were repeatedly and temporarily relieved with use of vitamin B concentrates began gradually to show a residual degree of spastic ataxia and eventually motor paralysis, with reflexes present. Definite histologic lesions of the central nervous system were observed in all but one animal. Nissl stains of the cerebral and Purkinje cells and of the ventral horn cells revealed evidence of degeneration. Weigert-Pal stains of the spinal cord showed definite loss of myelin in seven dogs. The peripheral nerves of three dogs showed an increase of material staining with scarlet red or by the Marchi technic. Observations on the effects of partial starvation, of supplements of cod liver oil and of therapy with dried yeast on the morphologic changes in the central nervous system were rendered inconclusive because, probably, the basic deficiency was not sufficiently prolonged to produce morphologic changes in the nervous system of any of the animals in such experiments. FROM THE AUTHORS' CONCLUSIONS. [ARCH. PATH.]

SPHENO-OCCIPITAL CHORDOMA. S. E. GOULD, Arch. Otolaryng. **23**:588 (May) 1936.

Only twelve of the fifty-two cases of spheno-occipital chordoma have been reported in the American literature. The symptoms in cases of cranial chordoma are due to impairment of function of the cranial nerves or to compression of the brain stem or spinal cord in the region of the foramen magnum. Frequently there is a history of trauma. In cases of nasopharyngeal tumor the prognosis is variable, depending on involvement of the brain or spinal cord. In cases of chordoma of the cervical portion of the spine the prognosis is poor. A man aged 68 was admitted to the hospital, with a growth in the left nostril. The tumor did not respond to surgical intervention, and a course of high voltage roentgen therapy was given. Radium was used. Biopsy revealed a benign epithelial polyp. This, however, continued to enlarge and was associated with headache, nosebleed and the loss of 26 pounds (11.8 Kg.). The patient refused permission for further surgical intervention. At autopsy a tumor was observed in the upper portion of the nasopharynx and the sphenoid and ethmoid cells. The diagnosis was malignant chordoma of the spheno-occipital region, invading the sphenoid and ethmoid sinuses and nasopharynx. Death occurred two years and nine months after the first symptom, of purulent basilar meningitis. There was no metastasis.

HUNTER, Philadelphia.

COMPOSITION OF PATHOLOGICAL CALCIUM DEPOSITS. DOROTHY R. MEEKER and H. D. KESTEN, J. Biol. Chem. **113**:289, 1936.

The composition of the inorganic salts in calcified deposits in the atherosclerotic aorta and in Mönckeberg's sclerosis was found to be similar to that of adult bone, thus confirming the earlier observations of Wells. Agar gel and sterile aortic tissue implanted in the peritoneum of rabbits underwent slight calcification, which was markedly increased by the administration of toxic doses of viosterol. The composition of these calcific deposits resembled the deposits in the aorta.

PAGE, New York.

HISTOPATHOLOGIC PICTURE OF METASTATIC ADENOCARCINOMA TO THE DURA MATER: RÔLE OF THE MICROGLIA. G. MARINESCO and M. GOLDSTEIN, Ann. d'anat. path. **12**:101 (Feb.) 1935.

Marinesco and Goldstein report a tumor metastatic to the dura mater from the breast in a woman aged 52. The tumor of the breast had been removed five years before. Cerebral symptoms were first noted three years after removal of the tumor. At autopsy a tumor the size of a nut was observed on the inner side of the dura mater, indenting the superior surface of the left hemisphere, 6 cm. from the occipital pole. The underlying cerebral hemisphere was edematous.

The tumor was attached by a short, wide pedicle. The neoplasm was surrounded by a fibrous capsule, which was torn in various places. This was probably the inner layer of the dura mater pushed out by the growing tumor.

Histologically the tumor was an adenocarcinoma, with typical acini. Surrounding the larger tumor were small microscopic nodules in the dura mater. Around these nodules were considerable perivascular infiltration and dilated vessels as well as occasional isolated tumor cells. Around the blood vessels and at a distance from these smaller tumor nodules were masses of cells which proved to be microglia cells. Among these cells were fragments of tumor cells. Similar microglial cells were also observed in regions where the tumor had undergone hyalination and necrosis. The cerebral cortex underlying the tumor showed degenerative changes in the ganglion cells. The cyto-architectonics of the cerebral cortex were disturbed. The nerve cells were flattened. In the cerebral cortex, especially where the tumor tissue came in direct contact, there was considerable dilatation of vessels, with infiltration of plasma cells in the neighborhood of the tumor tissue.

The observation of microglial cells in a tumor which does not contain any neural tissue confirms the theory of the mesodermal origin of the microglia cells and the hypothesis that they probably reached the tumor by a vascular route. It is assumed that the tumor cells irritated the surrounding tissues. This induced an inflammatory reaction and brought microglia to the tumor site, the rôle of these cells being to remove tissue débris.

SAVITSKY, New York.

HISTOLOGIC CHANGES IN CASES OF ACUTE DELIRIUM. J. TUSQUES, Ann. méd.-psychol. **91**:482 (Nov., pt. 2) 1933.

Microscopic studies were made of sections of the cerebral cortex from five patients who died of acute delirium. The lesions fell into two main classes: neuronophagia, especially in the frontal region, and neurolysis. Various degrees of neurolysis were seen, but the contours of the cell bodies were still visible. In extreme cases the cytoplasm was represented only by a fine dust when stained with Nissl's method. The nuclei resisted neurolysis longer and nuclear membranes persisted even when the cytoplasmic lysis was well advanced. The lesions were not attributable to alterations in the cadaver.

MOORE, Boston.

STUDIES ON PATHOLOGIC NEUROGLIA IN MAN: III. CEREBRAL ARTERIOSCLEROSIS. GASTONE CANZIANI, Riv. di pat. nerv. **46**:447 (Sept.-Oct.) 1935.

In ten cases of arteriosclerosis in which death occurred from cerebral hemorrhage, study of the neuroglia with the silver-bromoiodide method of Lugaro revealed that hypertrophy of astrocytes is not constant. When present, it bears no relation to age, severity of the disease or coma. Reticulocytic degeneration is at times present but is never marked. Granular degeneration is clearly demonstrable in only a few cases. The clasmatodendrotic degeneration at times presents features the same as those observed in normal brains and at times is atypical. No relationship is found between this degeneration and the duration of the coma.

FERRARO, New York.

CLINICO-ANATOMIC AND ETIOLOGIC CONTRIBUTION TO THE STUDY OF MEDULLARY NECROSIS. VIRGINIO PORTA, Riv. di pat. nerv. **46**:477 (Sept.-Oct.) 1935.

Porta reviews the literature of primary myelomalacia, which was first described in 1903 by Nonne under the term myelo-degeneratio-carcinotoxemica and later confirmed by others. Usually myelomalacia appears in cases of malignant tumor. The medullary compression in Porta's cases resulted from caseous pachymeningitis due to vertebral caries. These are the first cases described in the literature in which the origin was tuberculous. As regards pathogenesis, Porta believes that toxic material is liberated from the dura, producing leptomeningitis. This, in turn,

results in an increased permeability of the soft meninges, so that the toxins seep into the nerve parenchyma and attack the nerve elements. There are no inflammatory lesions in the cord tissue itself and no trace of primary vascular involvement.

FERRARO, New York.

CHANGES IN THE EPENDYMAL AND SUBEPENDYMAL ZONES OF THE BRAIN CAUSED BY RECENT HEAD INJURIES. J. GIERLICH, Deutsche Ztschr. f. d. ges. gerichtl. Med. **26**:100, 1936.

Changes in the walls of the cerebral ventricles and in their vicinity were observed in a large percentage of cases of cranial injury by blunt force. The changes were in the form of ependymal defects, hemorrhages about the defective and intact ependyma, either along the flat wall or the poles of the ventricles, and warty bulgings of the subependymal glia. The changes were ascribed to the alteration in hydrodynamic pressure within the ventricles occasioned by the trauma. In the presence of alcoholic intoxication or arteriosclerosis the ependymal injury was always extensive, even after minor trauma. The greatest part of the centrally located change was not visible to the naked eye and therefore had to be sought in the deeper zones removed from the direct or contrecoup lesions. Age seemed to play no factor in the condition since the lesions were equally severe in children and adults. Fatty changes were frequently present in the ependymal cells, even in persons who died immediately after their injury.

RUKSTINAT, Chicago. [ARCH. PATH.]

TUBERCULOMA OF THE BRAIN. IWAN RASDOLSKY, Ztschr. f. d. ges. Neurol. u. Psychiat. **154**:18 (Oct.) 1935.

Thirty-two cases of tuberculoma of the brain were found in the records of 13,039 autopsies from 1925 to 1934 performed in a hospital in Leningrad, to which adults only were admitted. Eleven of the 32 patients entered with a tumor syndrome, 14 with tuberculosis of the lungs and 7 with tuberculous meningitis.

In contrast to a recent opinion that the frequency of tuberculoma is decreasing, Rasdolsky noted that in Leningrad there has been no decrease in the last twenty-four years. Tuberculoma constitutes 16 per cent of all tumors in the autopsy reports of general hospitals. In Rasdolsky's series it constituted 14 per cent of all neoplasms. In 52 per cent of the cases in this series the condition caused no clinical picture of tumor but was discovered at autopsy. The incidence of tuberculoma was much lower in the reports from neurosurgical hospitals, varying from 2 to 3 per cent. Three of 146 tumors (2.1 per cent) in the Neurosurgical Institute of Leningrad were tuberculomas, and 0.36 per cent of 8,322 patients who died of pulmonary tuberculosis and tuberculous meningitis had tuberculoma. Seven, or 22.6 per cent, died of the tuberculoma; 4 (13 per cent), of pulmonary tuberculosis, and 20 (64.4 per cent), of tuberculous meningitis. Tuberculoma was therefore the cause of death in only 0.08 per cent of all cases in which the diagnosis at the time of admission was tuberculosis. Tuberculous meningitis, on the other hand, was the cause of death in 3 per cent of the cases.

There were 263 cases of tuberculous meningitis and tuberculoma; in 11 instances the condition was tuberculoma alone, in 21 tuberculoma and tuberculous meningitis and in 23 meningitis alone. In only 4.6 per cent of the complications of the central nervous system was there tuberculoma without meningitis. Most (75 per cent) of the tumors were solitary; 15 were supratentorial and 9 subtentorial. Two of the multiple tumors were supratentorial and 2 subtentorial. Four were both supratentorial and subtentorial. Of the supratentorial tumors 3 occurred in the frontal lobe, 3 in the parietal lobe, 1 in the temporal lobe, 2 in the thalamus, 1 in the caudate nucleus, 1 in the lenticular nucleus and 3 in the cerebral peduncle. Of the group of subtentorial tumors 4 were cerebellar and 4 pontile, and 1 was in the quadrigeminal plate. These tumors occurred more often in young patients; 40.7 per cent were in the third decade of life. The ratio of the incidence in males to that in females was 3:1. Rasdolsky asks the interesting question why tuber-

culoma is found so much more frequently in men than in women. He suggests that it may be due to the fact that men are more exposed to exogenous injuries, such as alcoholism, trauma to the head and, perhaps, infection. He assumes that all these factors in some way make the nervous system more vulnerable. He refers to cases in which tuberculoma arose a short time after trauma to the head.

Three of 4 patients on whom operation was performed died immediately after the operation, and 1 lived for seven months. Removal of deep-lying tuberculoma usually results in tuberculous meningitis. Patients do better with simple decompression. Rasdolsky, however, encourages radical removal of superficially placed tuberculomas. He collected 15 cases in which recovery followed this operation.

SAVITSKY, New York.

Psychiatry and Psychopathology

MENTAL DETERIORATION ASSOCIATED WITH CONVULSIONS AND HYPOGLYCEMIA. DANIEL C. DARROW, Am. J. Dis. Child. **51**:575 (March) 1936.

Darrow reports two cases of children with convulsions and mental deficiency in which there was encephalographic evidence of anatomic changes in the brain. Hypoglycemia occurred in both instances shortly after convulsions, but not after all convulsive attacks. In one case hypoglycemia of 20 mg. per hundred cubic centimeters could be produced by starvation without inducing a convulsive attack. Darrow suggests that the disturbance in the regulation of blood sugar may be secondary to the cerebral lesion.

WAGGONER, Ann Arbor, Mich.

PSYCHOPATHOLOGY OF TIME. PAUL SCHILDER, J. Nerv. & Ment. Dis. **83**:530 (May) 1936.

In primitive experience the sequence of moving objects and perpetual change in the environment produce the sense of time. Time is inside as well as outside oneself. It is both a perception of the outside world and a sensation experienced in oneself, but it is difficult to differentiate it from other experiences. Since perceptions are dependent on the anatomic and physiologic make-up, one must recognize that it is the psychic organism, with its emotions and drives, which determines the final structure of the perceptive world; time will be determined by the same factors.

It is known that the phenomena of déjà vu and depersonalization occur especially during fatigue. If life has become empty the experience of time changes also. Strauss described cases of depression in which time no longer moved. In cases of schizophrenia experience of time becomes senseless when libido is withdrawn from the world, and in many such instances time does not exist. Since the past is the time when action is not possible or necessary, it may become attractive in the form of history or fairy stories when there is fear of doing something in the present or future.

During intoxication from mescal and hashish time appears remarkably lengthened, but on looking back the period seems extraordinarily compressed. The disturbance in time perception is particularly outspoken in walking and seems connected with the optic experience of quick motion. Schilder concludes that some perceptions of time are disturbed and have become more primitive in function, with a distinct change in that of innate motion. Brush and Boring reported that a number of sleepers in a quiet community awakened between midnight and 5 o'clock and that the average error in the estimation of time was about 50 minutes. Hypnotized subjects estimated short periods of time exactly—even more exactly than patients in sleep. Time perception, like any other perception, can be repressed, as has been shown in cases of psychogenic amnesia.

It seems probable that the parietal lobe or adjacent parts of the temporal lobe in connection with the vestibular apparatus are important stations for the perception of sequences of time. The cortical lesions of Korsakoff's psychosis tend to confirm this idea. By analysis of the psychologic attitudes toward time, insight is gained into the status of the constructive energies of the person and their adjustment to reality.

HART, Greenwich, Conn.

A Statistical Study of Age in Relation to Mental Disease. Benjamin Malzberg, Ment. Hyg. **19**:449 (July) 1935.

On the basis of the age at the time of the first admission to the hospital, Malzberg reports a statistical study of mental disease in the state of New York for the three years ending July 1931. Ten years ago the average age at the time of admission to the institution was 43 years, while the present study shows an average age of 45 years. This rise is due chiefly to the increasing number of patients with cerebral arteriosclerosis, a group which represented 5 per cent of the first admissions in 1920 and 10 per cent in 1930. The average ages on admission for the various forms of psychosis were: senile dementia, 74 years; cerebral arteriosclerosis, 66 years; involutional melancholia, 53 years; paranoia, 50 years; alcoholism, 45 years; dementia paralytica, 44 years; manic-depressive psychosis, 39 years; dementia praecox, 34 years, and psychosis with mental deficiency, 33 years. The average age at the time of the first admission, classified according to sex, was 45 years for males and 46 for females.

Children (defined as patients under the age of 15 years) did not comprise a large group, constituting 159 of the 29,000 cases studied. The incidence of mental disease at this period, however, has increased for several decades. Of the children 30 per cent had disorders of conduct without psychosis, while 16 per cent suffered from psychosis with disease of the brain or other part of the nervous system. Of the hospitalized children in this study only 16 per cent had dementia praecox.

Of patients aged from 15 to 24 years, 57 per cent of the males but only 38 per cent of the females had schizophrenia. In the group of patients with manic-depressive psychosis 31 per cent were females and only 15 per cent males. In the age group of from 35 to 44 years only 8 per cent of the women and 25 per cent of the men had dementia paralytica. In this same age group a third of the women but only a fourth of the men had dementia praecox. In the age group of from 45 to 54 years dementia praecox had affected 26 per cent of the women but only 17 per cent of the men, while involution melancholia accounted for disease in 4 per cent of the men and 13 per cent of the women. This is balanced by the incidence of dementia paralytica, which affected 25 per cent of the men but only 7 per cent of the women. The difference between sexes in the distribution of involution melancholia begins to diminish after this decade, so that in the group of patients from 55 to 64 years 6 per cent of the men and 10 per cent of the women were afflicted with this type of psychosis. Above the age of 65, senile psychosis accounted for disease in one fourth of the men and one half of the women. Cerebral arteriosclerosis, however, remained more common in men.

Davidson, Newark, N. J.

Understanding the Drinker. Charles H. Durfee, Ment. Hyg. **20**:11 (Jan.) 1936.

Durfee believes that the intensified strain of the past few years is responsible for the current abuse of alcohol. By "problem drinker" is meant not necessarily one who drinks heavily but one who of himself cannot stop the drinking that has an injurious effect on his mental, physical or social life. Successful reeducation requires that the problem drinker come of his own free will, that he cooperate to the fullest extent, with entire confidence in the consultant, and that he be honest with the consultant and with himself. Discussion of problems to gain understanding of the motivations behind his conduct helps to reestablish his self-respect, counteracting the sense of humiliation or of inadequacy. Instead of continuing to permit alcohol to serve as a refuge from the world, the therapist must reeducate the patient so that he realizes his own personality as fully as possible within the limits of his capacities and his environment. Successful termination of therapy requires the patient's complete independence of the therapist.

The basic element of reeducation is the policy of encouragement; freedom and voluntary cooperation are far more effective than authoritarian measures. The

consultant waits until the patient sees for himself that he can solve his problem only by total abstinence. A subtle, indirect approach makes life so full and active that the problem of alcohol is crowded out by other interests. A temporary change of scene, with opportunities for a more satisfactory life, may prepare the patient to face the old environment successfully; if he must remain at home, a varied, flexible schedule of activities should be arranged to break into the old habits of drinking. In the initial stages the therapy requires practically twenty-four hour supervision, since reconstruction and readjustment of the whole person must be accomplished. Modern understanding of mental hygiene shows the drinker not as a moral weakling and an outcast but as a human being in need of readjustment. An educational program must inform the man with a potential tendency to alcoholism and the general public of the dangers of abuse of alcohol and the importance of self-control and self-responsibility in terms of scientific fact. A people endowed with inner harmony and wise in preventing the outer stresses that help to occasion drinking would be immune to alcoholism.

DAVIDSON, Newark, N. J.

MENTAL DEFICIENCY IN A CLOSELY INBRED MOUNTAIN CLAN. JACK MANNE, Ment. Hyg. **20**:269 (April) 1936.

In a Virginia clan surveyed by Manne large families live in barely furnished one room huts. Food is scarce and the diet poor; clothing and supplies are inadequate. Isolated, indifferent or hostile to strangers, with little interest in religion, recreation or culture, these people are ignorant of all that goes on outside their immediate world. Living under unhygienic conditions and lacking facilities for self-improvement, they are slowly undergoing racial disintegration. Excessive child bearing, privations and work under primitive conditions make life especially hard for women. A study of individual persons shows, nevertheless, the development of sturdy characteristics of personality, in spite of the unfortunate circumstances. Sympathy for suffering, devotion and a sense of responsibility can command the respect and obedience of the group.

Study of infection with hookworm in this region indicates that it is a prominent cause of physical and mental disease; poorly balanced, insufficient diet is another factor.

A careful analysis of inbreeding for several generations between members of a defective family, with many records of early death, feeblemindedness, congenital disease, tuberculosis and cleft palate, revealed conditions that resulted in many instances in early death, illegitimacy, drunkenness, murder, cancer, mental disease and poverty. This suggests the necessity of acquainting the more intelligent members of the community with the seriousness of the problem.

DAVIDSON, Newark, N. J.

STUDIES IN DEPRESSION. D. EWEN CAMERON, J. Ment. Sc. **87**:148 (March) 1936.

Six patients suffering from depression were shown an ambiguous figure of a staircase which fluctuated in appearance between that of a normal staircase and a staircase seen from below. The patients showed a slower rate of fluctuation than normal persons used as controls. As the illness tended to improve the rate of fluctuation tended to increase. Cameron concludes that in states of depression there is a constant flow of painful thoughts, ideas and feelings which, like any other powerful stimuli, produce inhibition of other activity. A similar observation was made on an excited and overactive patient. This patient was placed in a quiet room, and a record was made of his activity and talk. Ear-phones were then attached to his ears, and loud, harsh, penetrating sounds were introduced into the ear-phones. The patient at once became quiet and remained so for a considerable time. Thus, a strong stimulus inhibits activity, even though it may be extreme. A depressive reaction is an inhibition produced by the long-continued action of a strong stimulus.

Cameron tried to produce experimental depression by postulating that frustration is one of the most common causes of depression. He applied plaster casts to the hindlegs of guinea-pigs in extension. The degree of inhibition was measured by watching the respiratory rate of the guinea-pigs. Eighteen animals were used. At no time during the experiment was there any evidence of excitement. Cameron believes that a manic attack or excitement is a protection against forthcoming depression by breaking up the threatening inhibition. In nine of the guinea-pigs, clearcut inhibition was observed. Lesser degrees of inhibition were observed in the other animals. It is obvious that in some animals inhibition or depression is readily produced, whereas in others practically no inhibition results. On being exposed to a harassing situation only a certain portion of a group of animals shows depressive reactions.

Cameron believes that the central fact in depression is an abnormal preoccupation with a dangerous situation. Thus, the only animal which succumbs to a depression is one in which the capacity for adjustment is so slow and so inadequate that an abnormal degree of preoccupation with the situation becomes necessary. He realizes that his experiments are crude and that he cannot throw light on such phenomena as psychic pain, feelings of guilt and the necessity of repentance, all of which depend on the subject's previous experience. KASANIN, Chicago.

RELATION OF VITAMIN C PREDEFICIENCY TO NEUROPSYCHIATRIC CONDITIONS. H. BERSOT, Ann. méd.-psychol. (pt. 1) **94**:187, 1936.

Bersot outlines the most common manifestations of the predeficiency stage of vitamin C. Many "neurotic" disturbances are caused by hypovitaminosis and are relieved by the administration of vitamin C. Using the test of Harris and Ray, Bersot studied the elimination of vitamin C in the urine of normal persons and of patients with psychosis. In a normal person vitamin C is available to the point of saturation. A curve for the elimination of vitamin C for twenty-four hours plotted for several days shows a daily peak proportional to the amount of vitamin previously administered. In other words, all the vitamin taken in excess of the saturation point is excreted within twenty-four hours. Entirely different is the condition in many patients with psychosis. In a case of catatonia the amount of vitamin C in the urine was low. It remained low for many days in spite of the daily administration of 100 mg. of cevitamic acid. Only about fifteen days later and after the daily dose of vitamin C was doubled did the patient reach a vitamin C balance. Whenever the vitamin is withdrawn its amount in the urine falls; it takes, however, about eight days before the amount reaches the same level as before treatment. The same delay in reaching the saturation point was found in a case of senile melancholia; the patient's elimination of vitamin C became normal only at the end of a fortnight of the daily administration of 200 mg. of the vitamin. It is apparent, therefore, that patients with psychosis lack vitamin C. It is plausible that these patients produce an excess of oxidizing or reducing substances which destroy the cevitamic acid in the tissues. Bersot points out the importance of vitamin C predeficiency in minor psychiatric conditions and states that many patients with catatonia, arteriosclerosis and senility are affected with C hypovitaminosis. YAKOVLEV, Palmer, Mass.

STATES OF ALCOHOLIC INTOXICATION. HANS BINDER, Schweiz. Arch. f. Neurol. u. Psychiat. **35**:209, 1935; **36**:17, 1935.

Binder discusses the different states of disturbed consciousness associated with alcoholism. Stupefaction consists of quantitative weakening and increasing paralysis of psychic functions. Subjective consciousness, being phylogenetically younger than objective consciousness, is the first to suffer; loss of selfconsciousness is followed by release from inhibition of the more primitive impulses. As stupefaction deepens, perception and comprehension grow more difficult, while thinking becomes dull and, owing to lack of new impressions, repetitious. So long as there is some degree of mental activity, however, the subject is still able to orient

himself, though rather slowly and with difficulty. When objective consciousness is impaired to the degree that the mental functions are generally in abeyance, sopor or torpor supervenes, with complete unconsciousness as the end-stage. Physiologically, the process is a disturbance beginning in the phylogenetically youngest layers of the cortex and proceeding downward into the brain stem.

Whereas stupefaction represents a quantitative weakening of normal waking consciousness, delirium and the twilight state are qualitatively new experiences. Delirium is essentially a disintegration of consciousness, a dissociation of the component functions. Events of the environment being perceived in only a fragmentary manner, efforts of the subject to orient himself are only temporarily successful. Thinking is incoherent. This condition is not paralysis; on the contrary, there is a general increase in cortical irritability, in addition to the focal stimulation evidenced by illusions and hallucinations. The twilight state is a condition of narrowed consciousness in which the normal continuity of thinking is absent, and it is similar in many ways to normal sleep. Certain impulses otherwise suppressed manifest themselves in consciousness in the form of peculiar fantasies which lead to misinterpretation of the situation and, at times, to complete disorientation. The twilight state differs from stupefaction in that it represents a peculiar split-off, but not weakened, state of consciousness, and it differs from delirium in that the psychic interrelations are to a much greater degree retained.

Simple intoxication, which with some individual variation represents the normal reaction of man to indulgence in alcohol, is characterized at first by euphoria, lowering of the threshold to sensory stimuli and impulsive activity. This preliminary stage of excitement, which is rarely pronounced, is soon followed by one of stupefaction. The primitive impulses seldom manifest themselves to a high degree and are soon extinguished in the "descending" paralysis. Normal psychic relations and orientation are retained until the subject falls asleep. As the will remains sufficiently strong to keep behavior within certain bounds, acts foreign to the personality are seldom committed. For practical purposes, the subject must be regarded as legally responsible.

In addition to the acute effects of alcohol, individual disposition plays a part in abnormal intoxication. This form of intoxication is characterized by a prolonged state of marked excitement and abrupt and serious disturbance in the higher psychic functions; the personality is shaken to its depths, with consequent inability to exercise any effective control over behavior. The protracted excitement is succeeded within twelve hours at the latest by sleep. Complicated intoxication, one of the two main types of abnormal intoxication, differs only quantitatively from the simple variety. Although the subject remains in touch with his environment and his behavior can be understood by the ordinary observer, he is liable to fits of senseless rage, which may lead to violent deeds. Even the stage of deepening stupefaction may be punctuated by transient outbursts of excitement, occasioning blind acts of aggression. Slight delusional trends may be observed, but there are no hallucinations. Subsequent recollection of events may be incomplete, although total amnesia is about as uncommon as in simple intoxication. Legally, the subject should not be regarded as entirely responsible.

Pathologic intoxication, the other main form of abnormal intoxication, is further divided into the twilight and the delirious state. The onset is dramatically sudden in both these states, since the marked excitement and disturbance in consciousness become manifest simultaneously. The basic mood is one of anxiety. Orientation is fundamentally disturbed from the beginning, and the subject is entirely irresponsible. The behavior of a person in the twilight state often displays an element of the fantastic or unreal. Because of the anxiety, delusional misinterpretation of the situation and release of deeply submerged impulses, crimes of violence are frequent. In acute alcoholic delirium, on the other hand, such acts are rare because of the marked dissociation in both thinking and motor activity and the fleeting character of whatever ideas of reference may arise. The visual hallucinations characteristic of this state tend to appear in a mass and, for the most part, are dim and motionless.

In discussing the forensic aspects of the problem, Binder points out that, although the subject is legally irresponsible while in a state of pathologic intoxication, he may, according to Swiss and German law, be punished for becoming intoxicated if he should commit unlawful acts while in that state.

DANIELS, Denver.

CLASSIFICATION AND SIGNIFICANCE OF THE SCHIZOPHRENIC REACTIONS. M. SEREJSKI, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**:310 (March) 1935.

Serejski reports twenty cases of what he chooses to call schizophrenic reactions. All of the patients showed mental changes characterized by the relatively sudden onset of paranoid ideas, hallucinations and sometimes catatonic phenomena. The clinical picture resembled that of schizophrenia except that there was more confusion. The affective accompaniment of these delusional experiences was usually inadequate. In some cases there were hebephrenic features, with considerable transitory dilapidation and silliness. Serejski describes the paranoid, catatonic, hebephrenic, intermittent and simple forms of schizophrenic reactions, which resemble grossly the corresponding forms of dementia praecox. He emphasizes the constant presence in all these cases of a triad of etiologic factors, which, in his opinion, precipitated these transitory mental changes. In all cases there was: (1) somatic disease (infection, intoxication, endocrine crisis, severe parturition, etc.); (2) intense exhaustion due to overwork or malnutrition, and (3) acute or chronic psychic trauma.

The prepsychotic make-up of the patients was schizoid, and the physical habitus was asthenic. Epileptoid features were not infrequently noted in the parents. Most of the patients were intelligent, some even superior. While avoiding detailed discussion of predisposing factors, Serejski implies the existence of significant constitutional determinants.

The author suggests the term functional schizophrenia for these transitory, benign schizophrenic reactions and compares them with the functional hemiplegia of hysteria. Such disordered behavior patterns are frequently released by the concomitance of the etiologic factors already mentioned. The author assumes that schizophrenia is an organic disease of the brain. He also notes that occasionally organic disease of the brain may in its early stages precipitate schizophrenic reactions of this type, to be followed by the more characteristic organic reaction syndromes.

SAVITSKY, New York.

Meninges and Blood Vessels

ANOMALOUS VASCULAR LESION IN CEREBELLOPONTILE ANGLE: SEVERE NEURALGIC PAIN IN THE EAR AND PROFOUND NERVOUS DISTURBANCE; OPERATION AND RECOVERY. HAROLD I. LILLIE and WINCHELL MCK. CRAIG, Arch. Otolaryng. **23**:642 (June) 1936.

A case is reported of intractable pain in the ear, or tympanic plexus neuralgia. The patient had severe, intermittent neuralgic pain in the left ear, with increasing deafness and continuous dull ache over the left side of the head. Functional examination of the ears revealed profound nerve deafness on the left and hyperactivity of both vestibular labyrinths. The progressive unilateral nerve deafness suggested the possibility of a lesion in the cerebellopontile angle, although there was no corneal anesthesia, tinnitus, vertigo or loss of function of either labyrinth. Exploration of the left cerebellopontile angle was performed, and the site was thought to be normal until the operator noticed an anomalous artery looping over the eighth and under the ninth nerve. The ninth nerve was cut, and the artery was moved over, relieving pressure on the eighth nerve. The patient noted immediate relief on coming out of the anesthesia. There was dizziness for four days, but this disappeared. On the ninth postoperative day there were only anesthesia

of the nasopharynx and impairment of hearing. Six weeks later the patient said that hearing had returned to normal. This case is important as an illustration of the cure of neuralgia due to glossopharyngeal irritation caused by a lesion of the cerebellopontile angle.

HUNTER, Philadelphia.

DIPHTHERITIC MENINGITIS: REPORT OF A CASE AND REVIEW OF THE LITERATURE. F. G. CARLSON and H. W. MORGAN, J. A. M. A. **106**:1164 (April 4) 1936.

In a case of fatal meningitis due to the Klebs-Löffler bacillus inoculation of guinea-pigs showed the organism to be of a virulent strain. No similar cases could be found described in the English literature. The German literature contains reports of four cases. In the case reported the disease followed otitis media and mastoiditis.

FROM THE AUTHORS' SUMMARY. [ARCH. PATH.]

BENIGN LYMPHOCYTIC CHORIOMENINGITIS (ACUTE ASEPTIC MENINGITIS): A NEW DISEASE ENTITY. CHARLES ARMSTRONG and P. F. DICKENS, Pub. Health Rep. **50**:831 (June 21) 1935.

Owing to the results of recent experimental investigations, renewed interest has been aroused in the clinical syndrome variously called aseptic, idiopathic, epidemic or acute lymphocytic meningitis. This article presents the laboratory evidence for the etiology of this disease and summarizes all available evidence tending to prove that it is a new disease entity.

Acute aseptic meningitis was first described by Wallgren in 1926 and again by Viets and Watts in 1929. Subsequently, others have reported cases of the disease, and in 1932 Dickens asked the question: "Is this a new disease entity due to a filterable or nonfilterable virus?" The clinical picture of the disease is that of a benign infection characterized by headache, fever, meningeal irritation and cerebrospinal fluid under increased pressure, with a lymphocyte count above 50, associated with normal chloride, sugar and urea contents and a negative Wassermann reaction of the spinal fluid. The white blood cell count usually shows an increase, with fairly normal differential percentages, although not many observations have been made on the last-mentioned point.

Armstrong and Dickens state that the agent is in all probability a filtrable virus recovered by Armstrong and Lillie and reported in 1934 and 1935. The evidence for this began with the recovery by Armstrong of a virus which differed from any with which he was then familiar. It was encountered in the course of work on virus transmission in monkeys, and it is uncertain whether the infection originated independently in the animals used or was inoculated with material from a human source. Monkeys seem to be usually susceptible, as are mice and guinea-pigs, the infection producing in monkeys a uniform symptom complex similar to the human disease of so-called lymphocytic or aseptic meningitis.

Armstrong also demonstrated protective antibodies in the serum in a case in which recovery occurred. Shortly thereafter Traub recovered a virus from white mice which appeared to resemble closely the virus isolated by Armstrong. An exchange of protective serums was made, and it was shown that serum from guinea-pigs rendered immune to the Traub virus protected animals inoculated with the Armstrong virus and that serum from monkeys rendered immune to the Armstrong virus protected animals inoculated with the Traub virus. Rivers and Scott, of the Rockefeller Institute for Medical Research, also isolated a virus from two patients with meningitis which appears to be immunologically identical with the Armstrong virus. Further confirmatory work was done by Rivers, using his virus against the Armstrong, Traub and Rivers immune serums in tests on guinea-pigs. The results indicate the immunologic identity of the Armstrong, Traub and Rivers viruses. Armstrong and Rivers report several cases of acute aseptic meningitis in men and demonstrate that the blood serum of recovered patients protects animals from the virus. They suggest that this may be used to confirm the diagnosis.

In view of recent advance in the knowledge of its etiology, this disease, accurately designated as acute lymphocytic choriomeningitis, may be regarded as a

clinical entity due to a filtrable virus. This work is noteworthy and represents a triumph of the laboratory approach to the study of neuropsychiatric disorders. More investigations of this sort should be made on encephalitis, poliomyelitis and infectious mononucleosis, in which the central nervous system is sometimes involved.

EPSTEIN, Boston.

THE POSTERIOR SPINAL ARACHNOID FELTWORK: A TYPE OF ADHESIVE ARACHNOID REACTION OBSERVED IN MANY DISEASES OF THE SPINAL CORD. T. ALAJOUANINE, T. HORNET and R. ANDRÉ, Presse méd. **44**:691 (April 25) 1936.

The authors present the results of their study of so-called adhesive arachnoiditis, based on postmortem examination in thirty cases of various diseases of the nervous system in which the condition was present. Their material falls into the following three groups: syringomyelia, primary and secondary degeneration (Friedreich's and Marie's cerebellar ataxia and secondary degeneration of the cord in cases of hemiplegia) and infection of the nervous system (multiple sclerosis, acute anterior poliomyelitis, tabes, syphilitic myelitis and leprosy). They observed that the adhesive arachnoid proliferation forming a feltwork occurs exclusively in the posterior subarachnoid space of the spinal cord and never extends anteriorly beyond the dentate ligament. As a rule, this feltwork is most dense in the thoracic region, while in the cervical and lumbar regions the proliferative arachnoid reaction is usually slight and may be absent. This characteristic elective localization of feltwork in the posterior part of the thoracic region is independent of the localization of primary lesions in the cord itself. Thus, in cases of syringomyelia the cavities were observed in the cervical and bulbar regions—above the site of the arachnoid feltwork; in several cases of tabes the degeneration of the cord was confined almost exclusively to the lumbosacral region—below the site of greatest arachnoid adhesions; in cases of anterior poliomyelitis with widely scattered lesions in the ventral gray columns the arachnoid reaction was confined to the posterior thoracic subarachnoid space. The proliferative arachnoid reaction, however severe, does not cause secondary lesions in the spinal cord; in no cases studied did the authors observe evidence of marginal demyelinization in the tracts of the cord immediately underlying the posterior leptomeningeal feltwork. The observations were identical in all cases, whatever the type of primary disease of the cord.

The arachnoid feltwork is not of an inflammatory nature; in cases of primary parenchymatous degenerative lesion of the cord the feltwork gave no evidence of inflammation; in cases of tabes, in 50 per cent of which (6 of 12 instances) the spinal arachnoid proliferation was shown, and in association with infection of the nervous system the inflammatory reaction in the feltwork was present but was usually mild, appearing secondary to the adhesive proliferation of the arachnoid; moreover, it was not in topographic relationship to the specific inflammatory processes of various degrees of severity and chronicity observed elsewhere in the cord and meninges in this group of cases.

The arachnoid feltwork consists essentially of the proliferated fibrous lamellae of both the arachnoid and the pia. The term arachnoiditis is, therefore, inadequate. The adhesive leptomeningeal proliferation in the posterior subarachnoid space originates at the points where the two membranes—the pia and the arachnoid—are in continuity, i. e., where they form one membrane about the spinal nerve roots and their blood vessels, in the dentate ligament and especially in the dorsal ligament of Schwalbe, which is formed by the coalescence and local thickening of the pia-arachnoid on the dorsomedian line of the cord and is continuous with the pial septum inserted between the columns of Goll. The authors lay special emphasis on the outstanding rôle which this ligament plays in the pathogenesis of the arachnoid feltwork. They believe that the process is a pathologic exaggeration of the normal structurue and function of the dorsal ligament of Schwalbe. Serial sections of the cord show clearly that the feltwork represents primarily an abnormal proliferation of the leptomeningeal lamellae of Schwalbe's ligament.

This explains why the arachnoid feltwork is most marked in the posterior part of the thoracic region, where the ligament normally forms a thick continuous membrane, and is less marked in the cervical and lumbar regions, where the ligament consists of slender individual trabeculae or may even be entirely missing, and why it never occurs in the ventral subarachnoid space of the cord, where similar structure does not exist. They point out the functional significance of the dorsal ligament, which forms with the dorsomedian septum of the cord an important drainage system through which the products of parenchymatous disintegration are eliminated from the cord into the subarachnoid space.

The authors suggest that the excessive leptomeningeal proliferation and thickening of the dorsal ligament are the result of the reaction of the pia-arachnoid to the disease processes within the neuraxis. This proliferative leptomeningeal reaction does not develop suddenly and has no specific etiology; it may occur in time during the evolution of any long-standing disease of the nervous system, in association with disintegration of the neural parenchyma. This posterior arachnoid feltwork is defined as a general form of nonspecific, noninflammatory adhesive arachnoid proliferation, distinct from the inflammatory forms of arachnoid reaction, viz., the adhesive arachnoiditis following local lesions of the cord (tumor, abscess or epiduritis) or following primary meningeal infection (purulent meningitis). From the clinical point of view, except for roentgenographic (with iodized poppy seed oil) and manometric (Queckenstedt-Stookey) abnormalities, the posterior arachnoid feltwork has no clinical symptomatology of its own; its symptomatology is that of the underlying disease of the neuraxis. The authors question the therapeutic value of the various surgical procedures advocated for treatment of posterior arachnoid adhesions.

YAKOVLEV, Waltham, Mass.

Diseases of the Brain

ENCEPHALOMYELITIS FOLLOWING GERMAN MEASLES. H. HOUSTON MERRITT and YALE D. KOSKOFF, Am. J. M. Sc. **191**:690 (May) 1936.

The clinical history and findings in four cases of encephalomyelitis following rubella are reported. In addition, seven cases reported in the literature are analyzed. The great majority of patients were under 15 years, the ages varying from 5 to 33 years. The time of onset of involvement of the central nervous system averaged four days and varied from two to six days. The temperature was usually normal or only slightly increased; respiration was usually not affected. Neurologic signs and symptoms occurred with the following frequency: headache, as a presenting symptom, in six of the eleven cases, stiffness of the neck in four, attacks of unconsciousness with convulsive movements in seven, mental confusion in six, absence of deep reflexes in three and the Babinski sign in five. The cell count of the cerebrospinal fluid was increased, varying from 10 to 200 cells per cubic millimeter, with lymphocytes predominating; the protein content was moderately increased; the fluids were sterile. Although the pathologic lesions have never been carefully studied, it is suggested that they do not differ from the changes associated with encephalomyelitis following measles, as described by Greenfield. It is probable that the frequency is less than the 0.4 per cent given by Ford for that following measles. With the typical history of onset of mental or neurologic symptoms from two to six days after the rash, there is usually no difficulty in making the diagnosis. Only one of the eleven patients died, a mortality of 9 per cent, which is approximately equal to that (10 per cent) reported by Ford in encephalitis associated with measles.

MICHAELS, Boston.

ABDOMINAL PAIN AS SYMPTOM OF DISEASE OF THE BRAIN. I. S. WECHSLER, J. A. M. A. **105**:647 (Aug. 31) 1935.

Wechsler cites three cases that led to the question whether disease of the brain may not affect the visceral efferent pathways anywhere from the cortex through

the hypothalamus to the region of the vagus nerve in such a way as to manifest itself on occasion in the form of abdominal pain. What is known as abdominal migraine, a rather ill defined clinical syndrome, also came to mind, and the question arose as to the possible correlation of the abdominal symptoms with what is regarded as a cerebral condition. The occurrence of abdominal pain as an epileptic aura or after a convulsive attack or as the equivalent of a convulsion presented itself for consideration. The fact demonstrated by Cushing that solution of posterior pituitary injected into the ventricle gives rise to gastric hypermotility, pylorospasm and reverse peristalsis lent further plausibility to the assumption that abdominal pain may be a symptom of disease of the brain. These points, which are further supported by the experimental production of intussusception after ablation of the premotor cortex, justify the assertion that abdominal pain, without demonstrable intra-abdominal pathologic changes, may be regarded as a symptom of disease of the brain. That it is not rare can be inferred from the fact that in a comparatively short time Wechsler gathered sixteen cases. Migraine expressing itself in recurrent crises of abdominal pain, though neither common nor well defined, may possibly be the expression of fleeting cerebral pathologic changes. This view is fortified by the opinion commonly held that in some cases migraine is due to anaphylaxis and by the fact that the brain can react focally to sensitization. While encephalitis, because of its dissemination, cannot be lightly invoked as a basis for cerebral localization, it is a disease of the brain, and if abdominal pain can be shown to occur as one of its manifestations, the inference is justified that the pain is of cerebral origin. While hysterical or so-called psychogenic abdominal pain is generally vague and diffuse, it is not infrequently severe and sufficiently localized to simulate abdominal syndromes of one kind or another. It is neither a novel nor an uncommon experience to see hysterical patients who have been operated on one or more times for nonexistent gastric ulcer, disease of the gallbladder, appendicitis and the like. It may well be that actual disturbance of cerebral function, secondary to psychic emotional stimuli, is the underlying factor in the production of abdominal pain. In this sense psychogenesis merges into physiogenesis or neurogenesis. That sudden fright, for instance, can induce intestinal peristalsis and lead to diarrhea or contraction of the wall of the stomach and precipitate vomiting is a well known clinical fact. It may be debatable whether one is dealing in this case with cortical stimulation or cortical inhibition, but it is hardly to be doubted that one is concerned with a cerebral process probably involving in the circuit the cortex, the hypothalamus and the vagus nerve. Since it has been shown that abdominal pain can and does occur on stimulation or irritation or pathologic involvement of the cortex and possibly of other regions, it is probable that hysterical abdominal pain is the expression of a psychophysiogenic process and that the hysterical patient suffers neurogenic cerebral pain. In any case, vomiting related to a cerebral condition and abdominal pain are not altogether unrelated, and this may be equally true in cases in which there are demonstrable pathologic changes.

EDITOR'S ABSTRACT.

EXPERIENCES IN SUMMER EPIDEMICS OF ACUTE ENCEPHALITIS IN TOKYO. H. HASHIMOTO, M. KUDO and K. URAGUCHI, J. A. M. A. **106**:1266 (April 11) 1936.

According to Hashimoto, Kudo and Uraguchi, outbreaks in the summer and early fall of an acute febrile disease with a high mortality rate and peculiar symptoms resembling those of meningitis have long been known in Japan. The epidemic encephalitis occurring in St. Louis and Kansas City during the summer of 1933 has recently been reported to be similar to the Japanese B type in clinical, pathologic and epidemiologic features. This information seems to conflict with the erroneous contention of some authors that the Japanese B type is unique in Japan. During recent epidemics in Japan the authors encountered cases of encephalitis of the Japanese B type in Europeans and in an American, in concomitance with many other cases in Japanese inhabitants of the city of Tokyo. Toward the end of August 1935 there occurred a sudden outbreak of the same

type of encephalitis, with 1,362 cases reported in Tokyo by September 10. With the morbidity rate not more than 22 cases per hundred thousand of the population and the mortality rate less than 30 per cent, this epidemic has generally been regarded as much milder than the most severe epidemic of 1914, in Kagawa, Japan. To St. Luke's International Hospital two Russians and an American were admitted. After an illness with stormy course the two Russian patients died within a week, and the clinical diagnosis was verified by necropsy. The American, who showed a mild but typical clinical picture, was convalescing at the time of writing. All the patients were adults in the third or fourth decade of life. In three of them, who recovered, the onset of illness was rather abrupt, with high fever, severe headache and symptoms suggesting meningitis or encephalitis, while in two cases of fatal termination the initial rise in temperature was gradual, as in typhoid, and there was no evidence of involvement of the nervous system. These patients died within two days after a typical clinical picture of encephalitis had developed. Early diagnosis in such cases is difficult. The symptoms, clinical course, appearance of the spinal fluid and observations at necropsy are discussed. The clinical and pathologic manifestations in foreign patients with encephalitis were all comparable to those in many Japanese patients observed during the same epidemics in Tokyo. As a result of their experience in the recent epidemic in this city, the authors believe that they have further evidence that no clear distinction can be made between the Japanese B type and the reported St. Louis type. With regard to the etiologic factors little has been known concerning Japanese epidemic encephalitis. Long-continued exposure to the direct effects of sunlight, mental or physical fatigue in hot weather and like causes have been blamed as contributing etiologic factors in ushering in the illness. As the recent epidemic continued, however, through cooler weather, the aforementioned factors could not be held responsible for the onset of illness in many cases. As concerns the infective agent, the authors are now undertaking experimental studies similar to those reported by Webster and others in the St. Louis epidemic, which gave such successful results. As they have demonstrated experimentally that the disease can be easily transmitted to mice from patients who died of encephalitis and from mice so infected to successive series of healthy mice and that the infectious agent thus obtained traverses Berkefeld N candles, they are inclined to infer that the so-called Japanese B type and the St. Louis type are similar, not only in clinical or anatomic characteristics but presumably in the biologic nature of the infectious agent.

A Note on Laryngeal Vertigo. Douglas K. Adams, Brit. M. J. **1**:685 (April 4) 1936.

In 1876 Charcot described a group of cases of a condition which he termed laryngeal vertigo. Little has been written in the English literature concerning this condition. In the cases described the condition may be considered to fall into one of the following three groups: (1) coma following severe and prolonged coughing, accompanied by extreme dizziness and dyspnea; (2) laryngeal aura followed by coma and clonic movements of the limbs and other accompaniments of an epileptic seizure, and (3) a state similar to that in the case described in this article, in which a slight attack of coughing, preceded by a tickling sensation in the larynx, is followed by momentary coma without clonic movements of any kind. A man aged 35, whose history is reported, had a series of seizures after a severe cough of spasmodic nature. In each instance the attack of coughing was initiated by a tickling sensation in the larynx. The attacks of coughing were of two types. The more frequent attacks consisted of severe coughing, in which it was necessary to hold on to furniture to keep from falling. At this stage there was slight insecurity. When the cough subsided there was severe, generalized shaking of the body and limbs. The other type occurred less frequently and was initiated by the same tickling sensation. A slight cough, repeated three or, at most, four times, was followed by a fall and momentary unconsiousness. The patient often felt sleepy after an attack. Therapy with phenobarbital and bromide was of no avail.

Adams points out that in certain cases drowning may be caused by attacks of this nature. It seems possible that a few drops of water in the larynx in susceptible persons may cause a temporary loss of consciousness, resulting in death.

BECK, Buffalo.

NEUROLOGICAL COMPLICATIONS OF THE THIRD MOLAR TOOTH. C. BOWDLER HENRY, J. Neurol. & Psychopath. **16**:97 (Oct.) 1935.

Henry collected from the literature and private sources 700 cases in which eruption of wisdom teeth was complicated with symptoms of other conditions, and in many instances he found that the symptoms were neurologic rather than dental. The most common complication was facial neuralgia resembling tic douloureux. Roentgenography of the teeth in such cases revealed an impacted or buried third molar or a supernumerary denticle which exerted pressure and eroded the wisdom tooth. Complete cure of the neuralgia resulted after extraction of the tooth. In other cases neuralgic pains resulted from pressure on the second molar by a badly placed wisdom tooth which frequently lay horizontally. Another frequent complication was that of headache, which was usually in the occipital or the parietal region. This symptom was sometimes accompanied by vomiting, fatigue, loss of consciousness, pain referred to the lumbar region and lingual and supra-orbital neuralgia. In such cases the condition was often diagnosed as migraine. Less frequent complications were pain referred to the arm and shoulder and even to the lower extremity, paralysis and spasms, mostly facial, vertigo, nystagmus of the head, epileptic seizures and herpes and other cutaneous eruptions on the face, with definite distribution. In all these cases a diagnosis was made only by roentgenographic examination of the teeth. N. MALAMUD, Ann Arbor, Mich.

MENINGEAL LIPOMAS IN THE FORAMEN MAGNUM. WALTER MISCH, J. Neurol. & Psychopath. **16**:123 (Oct.) 1935.

Two cases of lipoma in the foramen magnum are reported: The first was that of an extradural lipoma covering the ventral surface of the lower part of the pons, the entire medulla and the upper portion of the cervical region of the cord. Symptoms were of one and a half years' duration, the onset being characterized by headache and cerebellar disturbances with the gradual development of signs of bulbar paralysis, affection of the cranial nerves, disturbance of the bladder and paraplegia. Death resulted from paralysis of the respiratory mechanism. The second case was that of an intradural lipoma covering the ventral and upper part of the medulla on the right side. The symptoms were of four years' duration and were essentially similar to those in the preceding case. Misch concludes that, although headache and cerebellar signs without the presence of papilledema characterized the onset, there are no characteristic signs to help differentiate lipoma from other extrabulbar tumors. MALAMUD, Ann Arbor, Mich.

AGENESIS OF THE CORPUS CALLOSUM IN MAN. M. SEGAL, South African J. M. Sc. **1**:65 (Sept.) 1935.

Agenesis of the corpus callosum is rare, less than one hundred cases having been reported. Although in many cases varying degrees of mental defect are presented, complete absence of the corpus callosum is often compatible with normal mental and physical existence. The first specimen described by Segal was the brain of a European man aged 55, who died of pulmonary tuberculosis. Complete absence of the corpus callosum was discovered at the dissecting table. In addition, the striae lancisii, septum pellucidum, indusium griseum, fascia dentata, hippocampal commissure and the massa intermedia were missing. The anterior and posterior commissures were of normal size. The fimbria and fornix coursed beneath the roof of the lateral ventricle. No nodular sclerosis or hydrocephalus were present. The mesencephalon and rhombencephalon were normal.

The second specimen was the brain of a European infant who died three days after birth. The mother was weak, labor was difficult, the feet presenting. The entire corpus callosum was missing, the roof of the third ventricle being formed by meninges and the anterior wall by a thin lamina terminalis. The lateral ventricles were enlarged. No rhinencephalic structures were present, the olfactory bulb and tract, fimbria and fornix being absent.

The third specimen was the brain of a European woman aged 24, who died of puerperal sepsis. In her case there was almost complete defect of the corpus callosum, the two hemispheres being united by overexpansion of the gray matter of the lamina terminalis and gyrus cingulus. This junctional area was dorsal to the massa intermedia and was composed of gray tissue with islets of white fibers. The fimbria arose normally but was lost in the roof of the lateral ventricle. There was no posterior crus or hippocampal commissure. The gyrus dentatus was rudimentary and the septum pellucidum absent.

Segal discusses the evolution of the corpus callosum as an expansion of part of the hippocampal commissure to serve as a connection between the neopallium, or nonolfactory cortex of the two hemispheres. Anatomically, the fibers of the corpus callosum unite both homologous and heterologous cortical areas and serve physiologically to mediate association impulses essential to higher cortical correlation. Experimental work has demonstrated grave disturbances in behavior in the nature of apraxia, apathy and inhibition as a result of transection of the corpus callosum. These disturbances are, however, transient. Clinical observations in cases of tumor of the corpus callosum have often failed in part to demonstrate these symptoms.

The impermanence of symptoms of transection of the corpus callosum, the frequent failure of its pathologic destruction to produce the expected symptoms and the total absence of symptoms in cases of agenesis, such as those reported in this paper, imply that loss of this structure may be compensated for by the establishment of pathways in the brain which functionally replace the missing commissure. One fact stands out: "that the human brain can and does adequately compensate for the lack of . . . the corpus callosum in a manner closely analogous to the establishment of a collateral circulation in the arterial system."

MACKAY, Chicago.

ARTERIOSCLEROSIS OR CEREBRAL SYPHILIS? AUTOPSY. ROUVROY, J. belge de neurol. et de psychiat. **35**:650 (Nov.) 1935.

To illustrate the difficulty of the differential diagnosis of arteriosclerosis and syphilis of the central nervous system, the author describes the case of a woman aged 51, who had suffered a series of cerebral vascular accidents, which were followed by weakness of one or both extremities on the left, with gradual improvement in the weakness after each attack. Finally, she had an attack involving the left side which warranted hospitalization. Before this time gradual, mild, progressive mental deterioration had been noted. At the time of examination there were: deficit of intellectual aptitude, more or less expressionless features, mild left hemiparesis, some dysarthria and a general picture of organic dementia. The spinal fluid was normal except for a slight change in the colloidal benzoin reaction. The Kahn reaction of the blood was negative. After the last attack the patient showed little change until the sudden onset of intense dyspnea and cardiac distress, with ensuing death. The cause of death was diaphragmatic hernia. General examination revealed little of interest except the diaphragmatic hernia and mild generalized arteriosclerosis. Histologic examination of the brain revealed chronic leptomeningitis, with lymphocytic round cell infiltration of the blood vessels of the meninges, endarteritis of the small vessels of the cortex and hyperplasia of the intima of the arteries of the pia mater and of the arteries at the base, with atherosclerosis and infiltration of the adventitia. In view of these observations, Rouvroy concludes that the patient had syphilis of the central nervous system in spite of the negative serologic reaction.

WAGGONER, Ann Arbor, Mich.

ETIOLOGY OF THE SYNDROME OF THE SPHENOID FISSURE AND THE APEX OF THE ORBIT: EFFICACY OF ANTISYPHILITIC TREATMENT. H. ROGER and J. ALLIEZ, Rev. d'oto-neuro-opht. **13**:245 (April) 1935.

The syndrome of the sphenoid fissure and apex of the orbit results from: neoplasm, disturbances of an undoubted syphilitic origin and a third group the etiology of which is uncertain. It is in the third group that Roger and Alliez have found antisyphilitic treatment often of great benefit. The study comprises fifteen cases, in seven of which the condition was caused by neoplasm. In the remaining eight instances the ages varied from 31 to 72 years. In only one case were signs of syphilis exhibited, and in this instance the Bordet-Wassermann reactions of the blood and the spinal fluid were negative. In seven of the eight cases the condition was cured, and in one it was improved. The cure was sometimes rapid, in three or four weeks, but it was usually slow, requiring three, six or ten months, if treatment was prolonged. These results are contrary to those obtained by a number of other investigators, even in some cases in which the origin was undoubtedly syphilitic. In spite of the lack of clinical evidence of syphilis, Roger and Alliez incriminate syphilis to explain their success with antisyphilitic treatment in these cases. The lack of success of other observers is attributed to too short a course of treatment or to a different anatomic substratum. Active and prolonged antisyphilitic treatment is recommended in all cases in which the origin is not determined.

DENNIS, San Diego, Calif.

INTRACRANIAL HEMORRHAGE AFTER HEAD INJURY WITHOUT FRACTURE OF THE SKULL. G. JUNGMICHEL, Deutsche Ztschr. f. d. ges. gerichtl. Med. **26**:130, 1936.

Intracranial hemorrhage was encountered in 5.6 per cent of persons who had head injury but no fracture of the skull. Jungmichel explains extradural hemorrhage without skull fracture in young persons on the basis of cranial elasticity—the bone being able to bend under a blow. The tight dura, however, is torn from its bony bed by the blow, and a tear in the vessels on its exterior surface results in hemorrhage. The bleeding is primarily from arteries, the accompanying veins contributing only slightly. Fissures of the skull must be ruled out by roentgen examination, postmortem inspection and, if necessary, maceration of the suspected bone.

Subdural hemorrhage occurs from arteries, large venous sinuses and torn meningeal veins. Only slight trauma is necessary to induce such bleeding, and there is no basis for the statement that such accidents occur typically only in boxers. Similar lesions may be found in the football player struck on the head with a rain-soaked ball.

The intracerebral lesions were various and at times seemed associated with the site of action of the direct force; at other times contrecoup lesions were apparent. Some of the injuries seemed dependent on the glancing character of a blow; others, on the transmission of the force wave through the fluid in the lateral ventricles.

RUKSTINAT, Chicago. [ARCH. PATH.]

Diseases of the Spinal Cord

NERVOUS COMPLICATIONS FOLLOWING SPINAL ANESTHESIA: CLINICAL STUDY OF SEVEN CASES, WITH TISSUE STUDY IN ONE INSTANCE. SAMUEL BROCK, AARON BELL and CHARLES DAVISON, J. A. M. A. **106**:441 (Feb. 8) 1936.

Brock, Bell and Davison report seven instances of neural complications following spinal anesthesia, with tissue changes in the spinal cord in one case. In all but one of the cases the cocaine derivative used was known; two received a preparation of procaine with strychnine sulfate, three nupercaine and one procaine hydrochloride. The site of injection was the lumbar subarachnoid space between

the second and the third lumbar vertebra or lower, except in one instance in which the injection was made between the first and the second lumbar vertebra. There were two instances of aseptic meningitis, one of polioencephalitis, one of lumbar radiculitis, two of cauda equina neuritis and "myelitis" and one of transverse "myelitis." The time elapsing between the spinal anesthesia and the appearance of the neural complications varied from almost immediate onset to an interval of three weeks. Clinically, in the two cases of aseptic meningitis there was a rapid and benign course, ending in complete recovery. In one instance of cauda equina neuritis and myelitis and in the case of transverse myelitis the illness ended fatally, owing to complications directly attributable to the neural disease, twenty-nine months and three months after the onset, respectively. The clinical course in the first case was characterized by long periods during which the condition was stationary; these periods were followed by spread of the process to higher levels of the cord. The most severe pain occurred in the patient with lumbar radiculitis, with slight residual signs sixteen months after the onset. One of the patients with cauda equina neuritis and myelitis regained the ability to take a few steps five months after the onset, but the control of the sphincters and the sensory and reflex status remained unchanged. In the instance of polioencephalitis, life was despaired of early in the illness; the patient recovered, however, but still had residual signs nineteen months after the onset. The spinal fluid showed no characteristic picture. In all the cases but one (that of lumbar radiculitis) the neural syndrome so speedily followed the administration of the spinal anesthetic as to suggest a direct chemotoxic effect of the cocaine derivatives on the neuraxis. However, the direct chemotoxic effect does not entirely explain the causation of the neural complications. There is the undeniable fact that in the great majority of patients on whom operation is performed with the use of spinal anesthesia complications of the central nervous system do not develop. Furthermore, instances like that of lumbar radiculitis, in which the interval between the anesthesia and the onset of symptoms was relatively long, and that in which cauda equina neuritis and mild involvement of the cord continued over a period of months, terminating in fatal transverse myelitis, suggest the possible intervention of other factors. To account for the relative infrequency of neurologic complications following spinal anesthesia, one has to assume the existence of tissue sensitivity to the cocaine derivatives. A consideration of the difference in the cellular reactions of the spinal fluid in the two instances of meningitis adds weight to the belief that factors other than those of chemotoxic nature participate. In this connection the close resemblance of the condition in the case of lymphocytic meningitis to that in the cases described by Abramson is of special interest, since his review of the evidence concerning the etiology is much in favor of a virus. The tissue changes in the spinal cord in the case of transverse myelitis are those characteristic of toxic myelopathy and are similar to the changes in the few cases already mentioned in the literature. Spinal anesthesia has been successfully used in so many diverse conditions that the associated disease can have no causative relationship to the nervous complications. Allergic factors are not involved in these cases, since one is not dealing with protein sensitization. At present there is no way of determining whether or not a patient's nerve tissues are oversensitive to the cocaine group of anesthetics; or is anything but an unsatisfactory symptomatic therapy available once nervous complications arise. For these reasons, it is strongly urged that spinal anesthesia be restricted to a special group of patients unable to withstand the risks of a general anesthetic.

EDITOR'S ABSTRACT.

LESIONS OF THE SPINAL CORD AFTER RACHITIC KYPHOSCOLIOSIS. A. PONSOLD, Arch. f. Psychiat. **103**:199 (May) 1935.

Ponsold reports the case of a man aged 21 who suffered from kyphoscoliosis for ten years. During the last few weeks before admission to the hospital there developed spastic paraparesis of the legs, accompanied by anesthesia

from the seventh to the tenth dorsal segment and hypesthesia from the tenth dorsal segment to the toes. Roentgenograms showed scoliosis, with the convexity to the left. Lumbar puncture and injection of iodized oil showed block at the level of the eighth and ninth dorsal vertebrae. Some of the sensory disturbances apparently were produced by pressure on the dura, and the anesthesia was probably produced by traction on the roots. The part of the cord which was nearest the convexity was affected much more severely than the other side and thus produced an incomplete transverse lesion. Laminectomy was followed by slow and incomplete disappearance of the clinical signs.

W. MALAMUD, Iowa City.

ACUTE AND SUBACUTE EPIDEMIC NEUROMYELITIS. A. AUSTREGESILIO, Deutsche med. Wchnschr. **62**:48 (Jan. 10) 1936.

Austregesilio had opportunity to observe an epidemic of neuromyelitis for three years in Brazil. This epidemic, obviously of infectious origin, began in 1928 and reached its peak in 1933. It was most serious in the coastal cities and tended to occur chiefly in the winter months. There was no social or racial predisposition, but in the majority of cases the disease occurred between the ages of 30 and 50 years. In forty-nine cases diagnosis had been made in Brazil. The mortality rate ran as high as 32.6 per cent. The manner of transmission was not determined.

Clinically the course of the disease had three stages. The first stage began with general symptoms of a griplike infection, followed by polyneuritic manifestations: pain, paresthesia, flaccid paralysis and a moderate degree of fever. Objective sensory disturbances were rare at this stage. Some patients recovered at this point, while others passed into the second stage, characterized by more severe symptoms of acute myelitis, with ascending motor and sensory disturbances, the latter often being segmentally distributed, and by paralysis of the sphincters and trophic ulcers. At this stage the paralysis often remained flaccid with loss of all reflexes, but occasional signs of disturbance of the pyramidal tract appeared. Vasomotor symptoms in the form of edema, increased sweating, congestion and cyanosis occurred in some cases. The second stage became chronic, or the patient progressed into the third stage, in which advanced cachexia, paralysis of the medulla oblongata and often death occurred. Some patients died within forty-eight hours after the onset, others much later. Examination of the blood revealed polynucleosis in many cases. The spinal fluid sometimes showed increase in the protein content, with or without an increase in the cell content. Xanthochromia was occasionally observed.

No micro-organisms could be stained or cultured. Scarification of the cornea of the guinea-pig with spinal fluid caused ulceration and formation of a profuse serous exudate. Intracerebral injection into guinea-pigs of an emulsion of the spinal cord and nerves obtained from patients produced encephalitic phenomena and sometimes death.

Pathologically, there were punctate hemorrhages and congestion of the nerve tissues. Inflammatory processes in the spinal cord consisted of generalized and perivascular lymphocytic infiltration. Degenerative disease of the ganglion cells was observed in the cells of the anterior horn, with gliosis. The peripheral nerves were also the seat of lymphocytic infiltration as well as primary and secondary degenerative changes.

MACKAY, Chicago.

Vegetative and Endocrine Systems

MEDULLARY TUMOR OF THE ADRENAL GLANDS, WITH HYPERTENSION AND JUVENILE ARTERIOSCLEROSIS. D. N. KREMER, Arch. Int. Med. **57**:999 (May) 1936.

A case of arteriosclerosis and hypertension in a girl aged 14 is reported by Kremer. The patient had had attacks of coughing, facial edema and dyspnea and gave evidence of nephritic retinitis with albuminuria. The blood pressure

varied, often being above 150 systolic and at one time reaching 206 systolic. She died in stupor. Autopsy revealed aortic atherosclerosis, myocardial hypertrophy and degeneration of the hypertensive type, neuroma ganglionare in both adrenals, thrombosis of the vessels of the left cerebral hemisphere and atrophy of the optic chiasm. Both adrenals were greatly enlarged. The cortex had been thinned, and it encircled but did not include the tumor. Most of the adrenal medulla was replaced by a red-brown mass of paragangliomatous tissue. These neoplasms were apparently responsible for the hypertension. Kremer suggests that the occurrence of hypertension in the young should always arouse suspicion of a chromaffin tumor of the adrenal gland. DAVIDSON, Newark, N. J.

A CENTRE, OR CENTRES, IN THE HYPOTHALAMUS CONTROLLING MENSTRUATION, OVULATION, PREGNANCY, AND PARTURITION. G. W. THEOBALD, Brit. M. J. **1**:1038 (May 23) 1936.

The purpose in this communication is to advance evidence of a clinical nature in favor of the thesis that there are centers in the brain, probably in the hypothalamus, which control menstruation, ovulation, pregnancy and parturition. It is suggested that this center receives afferent stimuli from: (1) the ovaries (of hormonal nature), (2) the external generative organs (by nervous paths) and (3) the special senses and psyche (psychologic). The efferent impulses operate through the anterior pituitary gland and generative organs.

All rhythmic bodily functions are regulated through cerebral centers. The regularity of the menses suggests such control. On the other hand, amenorrhea may be caused by mental strain or fear. That the menstrual cycle can be modified by hypnosis and that menstruation frequently ceases in women who are addicted to the use of drugs, to return when they are cured, are further evidences of cerebral influence. It is suggested that ovulation, pregnancy and parturition are similarly controlled, the centers being presumably in the hypothalamus.

It is postulated that the afferent stimuli to the menstruation center are provided by the ovarian hormones, by nervous stimuli from the generative organs and by the cerebral cortex. The efferent stimuli from the center operate through the anterior pituitary gland and, to a certain extent, through nervous impulses to the generative organs. It then follows that the correct method of treating menstrual disorders in the majority of cases, provided that the ovaries and anterior pituitary gland are normal, is to treat the center directly by suggestion or indirectly by promoting the general well-being of the body by dietetic and hygienic measures.

BECK, Buffalo.

THE ANTI-KETOGENIC SUBSTANCE AND PHLORHIZIN DIABETES. P. T. BLACK, J. Physiol. **84**:15 (April 26) 1935.

It has been shown that rats treated with extract of anterior pituitary containing the ketogenic principle become resistant to its action and that the serum of these treated animals, when injected into animals which were not treated, confers on them marked resistance to this hormone. It is believed that prolonged treatment stimulated the production of an antiketogenic substance. It has also been shown that hypophysectomy reduces the ketonuria of depancreatized or phlorhizinized dogs. Black showed that the removal of the pituitary of depancreatized dogs leads to a sharp decrease in the secretion of ketone bodies. It has also been shown that fasting phlorhizinized rats excrete large quantities of ketone bodies in the urine. Black undertook to determine the nature of this acquired resistance to the ketogenic action of pituitary extract by the study of phlorhizin diabetes in animals exhibiting this resistance. He treated female rats with daily injections of anterior pituitary extract for from three to four months. From time to time the animals were placed in metabolism cages and fasted for two or three days. During this test period each animal received daily 1 cc. of anterior pituitary extract per hundred grams of body weight. Five of six continuously treated ani-

mals showed insignificant amounts of acetone in the urine even after four days of fasting and with intensive phlorhizin poisoning, while all six of the animals used as controls suffered severe ketosis. It was found that about three months of continuous treatment was required to bring about complete loss of sensitivity to the 1 cc. dose. The animals used as controls which received no injection of the hormone did not become resistive to the ketogenic hormone. A similar experiment was carried out, using large doses of phlorhizin (300 mg. daily). The resistant animals during this test excreted various amounts of acetone, while the mortality among the control animals was exceedingly high. Black showed that the rats which lost power to respond to pituitary extract by the development of acetonuria also became insensitive to the acetone-producing effect of phlorhizin poisoning. He ascribes both these alterations of metabolism to the presence of the anti-ketogenic substance. His experiments seem to show that: (1) the ketogenic principle of the anterior pituitary is secreted and plays a part in the production of acetonuria during phlorhizin diabetes; it is therefore a physiologic hormone and not merely a pharmacodynamically active substance; (2) the acquired resistance to the injected ketogenic principle of bovine origin is accompanied by acquired resistance to the autogenous ketogenic hormone discharged by the pituitary in the experimental animals and therefore is not specific for the bovine hormone.

PALMER, Philadelphia.

CHANGES IN THE PITUITARY GLAND OF THE GUINEA-PIG DURING AND AFTER LABOR. MICHEL WEIS, Rev. franc. d'endocrinol. **13**:195 (June) 1935.

The aim in this study was to ascertain the changes in the hypophysis of female guinea-pigs during the stage of labor and afterward. A study of the hypophyses of twenty-five guinea-pigs in the second month of pregnancy was made as a control. In this material there was an increase in the weight and volume of the glands. The islets and pseudo-alveoli contained large quantities of colloid. The cells were of the eosinophilic type. In addition, cellular débris and evidence of active regeneration were observed; numerous mitotic figures were seen especially in the anterior lobe.

In fifteen female guinea-pigs killed at the moment of labor the alveoli were hypertrophied; the cellular elements were chiefly chromophobic and were enlarged and had a fine granular appearance. No cyanophilic cells were seen, while eosinophilic cells were still present in large numbers. Twenty-four hours after labor only chromophobic cells with vesicular clear nuclei were to be seen. An occasional eosinophilic cell was observed, while the cyanophilic cells were no longer existent. No colloid substance could be seen in the vesicles or in the vessels. Forty-eight hours after labor eosinophilic cells reappeared, while the colloid substance was seen again about sixty hours after delivery. At about the same time chromophobic and chromophilic cells were also discernible. About ten days after labor the pituitary gland regained its normal appearance.

In summary, one may state that the anterior lobe of the pituitary gland of the guinea-pig is composed strictly of chromophobic elements immediately after labor and for a period of twenty-four hours subsequently. No colloid can be observed during this period. Weis states that these striking changes in the pituitary are not caused by the inhibitory influence of the corpus luteum or by the products of the placenta and fetus. He also denies that the changes are responsible for the induction of labor. He suggests the possibility of the influence of the posterior lobe or of the nervous system proper on parturition and ascribes to the anterior lobe the induction of lactation.

NOTKIN, New York.

INFLUENCE OF THE VEGETATIVE NERVOUS SYSTEM ON THE ACTIVITY OF THE HYPOPHYSIS. I. A. DOUBOVIK, Rev. franç. d'endocrinol. **14**:151 (April) 1936.

This investigation deals with the influence of the nervous system on the activity of the anterior and the posterior pituitary lobe. The experiments were carried out

on immature frogs (Rana temporaria). In one series of experiments Doubovik stimulated the anterior pituitary lobe with the induced current for about two minutes every other day for two weeks. As a result of the stimulation accelerated maturation of the roe took place. Frogs of the same age used as controls showed no change. Doubovik therefore believes that the acceleration in maturation of the ovaries resulted from increased secretion in the anterior pituitary lobe. Stimulation of the stellate ganglion caused no change in twenty-five experiments. In order to determine whether he was dealing with a lack of influence on the anterior pituitary or whether the secretion of the hypophysis was inhibited by stimulation of the sympathetic ganglion, Doubovik stimulated the medulla in the region of the vagus nerve. Again a series of twenty-five experiments revealed no change; the ovaries remained filled with immature roe. Doubovik therefore draws the conclusion that stimulation of the sympathetic and parasympathetic ganglia does not accelerate or inhibit the secretory activity of the anterior pituitary lobe. A similar investigation was carried out on the posterior pituitary lobe. Normal and hypophysectomized frogs were used. The expansion and contraction of the melanophores served as an indicator of posterior pituitary activity. In normal frogs stimulation of the stellate ganglion produced contraction of the melanophores; the skin became clear in from two to five minutes, and the outlines of the epidermis were pronounced, consisting of dark spots on a clear field. Stimulation at the base of the medulla caused expansion of the melanophores; the skin became uniformly dark. In order to exclude the possibility of transmission of electrical stimulation through the surrounding tissue, Doubovik extirpated the stellate ganglion bilaterally. This procedure caused clearing of the skin for from five to six hours after the operation. These frogs survived about two weeks and showed negative phototropism. Frogs in which bilateral vagotomy was performed became light in color. These frogs displayed positive phototropism. They remained alive ten days after the operation. In order to ascertain whether the change in pigmentation of amphibians depends on the activity of the posterior pituitary lobe, Doubovik hypophysectomized a number of frogs. After this procedure the epidermis turned light. He found that irritation of the stellate ganglion of hypophysectomized frogs did not render the epidermis clearer and that irritation of the medulla of these frogs did not cause expansion of the melanophores. In instances in which only the anterior lobe of the pituitary was extirpated the epidermis became brownish in a day or two. When the mixed and posterior lobes of these frogs were irritated mechanically the color remained dark, while the musculature of the genital organs of the female frogs became active. Doubovik came to the conclusion that the secretory activity of the anterior lobe of the hypophysis is independent of the nervous system. The hormonal activity of the posterior lobe is autonomous in character. The sympathetic system inhibits the secretion of the posterior lobe, while the parasympathetic system stimulates its secretion. The activity of the posterior lobe is independent of the hormonal activity of the anterior lobe. NOTKIN, Poughkeepsie, N. Y.

NYCTURIA AS A CENTRALLY CONDITIONED FUNCTIONAL DISTURBANCE OF THE VEGETATIVE SYSTEM. ARTHUR JORES and HELMUTH BECK, Deutsche Ztschr. f. Nervenh. **138**:4 (Aug.) 1935.

Nycturia is commonly associated with diseases of the heart and kidneys, enlargement of the prostate, acute yellow atrophy of the liver, Weil's disease, exudative pleuritis and diabetes. In these conditions it is usually considered to be due to a physical disturbance. Pophal reported a number of cases of nycturia observed during the war in association with nerve injuries and recovery from psychosis, which he ascribed to the poor nutrition that prevailed during that period. Polyuria is often present in nervous conditions. Oppenheim observed polyuria in a patient suffering from melancholia. Amelioration of the symptom paralleled improvement in the mental condition. Polyuria in a patient suffering from a lesion in the medulla was described by Ebstein. E. Meyer reported a case of cerebral syphilis associated with a similar disturbance. Hösch was among the

first to report a case of nycturia in a patient with cerebrospinal syphilis. A. Jores observed a number of cases of nycturia dependent on disturbances of the central nervous system. Beck observed a patient suffering from ulcer of the stomach in whom there later developed a tumor of the cerebellopontile angle. This patient had oliguria during the day and nycturia, with an output of urine up to 1,000 cc.

In this article Jores and Beck report the occurrence of nycturia in a number of cases of contusion of the brain. The symptom was observed in the acute stage during the first three or four days after the injury. The authors assume that nycturia is due to involvement of the vegetative nervous system, especially hyperirritability of the vagus nerve, since bradycardia was present. Beck's previous observations of nycturia in a case of ulcer of the stomach led the authors to more careful investigation of the subject.

According to Jores and Beck, nycturia is a frequent symptom in association with ulcer of the stomach. In these cases there is involvement of the vagus nerve and the vegetative nervous system. This is responsible for the nycturia. Jores, Kupler and Hochmann produced artificial nycturia by means of ergotamine and barbital. According to Hochmann this form of nycturia resembles the spontaneous type, even to the increased output of chlorides and nitrogen. Hochmann found that atropine controls nycturia. These findings indicate that the vegetative system, especially the vagal component, is an important factor in the genesis of nycturia.

BERNIS, Rochester, N. Y.

Treatment; Neurosurgery

MENINGITIS DUE TO TYPE I PNEUMOCOCCUS: REPORT OF A CASE WITH RECOVERY DUE TO SERUM THERAPY. CLARENCE K. WEIL, Arch. Int. Med. **57**:514 (March) 1936.

Pneumococcic meningitis is usually fatal, and since the type of organism is seldom determined serum therapy is often unsatisfactory. Weil reports a case in which a man sustained fracture of the skull in an automobile accident; shortly after there developed nasal leakage of spinal fluid. The patient blew his nose and almost immediately complained of severe headache. Within a few hours he had fever, stiffness of the neck and stupor; the spinal fluid was cloudy and loaded with polymorphonuclear cells. Type I Pneumococcus was seen in the fluid. Felton's concentrated antipneumococcus serum of types I and II was injected both intraspinally and intravenously. For eight days the patient received from 10,000 to 30,000 units a day given in two or three intravenous injections and during the same eight day period five intraspinal injections of 10,000 units each. The fluid was sterile by the fifth day, and the patient eventually made an excellent clinical recovery.

DAVIDSON, Newark, N. J.

CERVICAL SYMPATHECTOMY IN RETINITIS PIGMENTOSA: PRELIMINARY REPORT ON RESULTS. GÉZA DE TAKÁTS and SANFORD R. GIFFORD, Arch. Ophth. **14**:441 (Sept.) 1935.

In the past few years cervical sympathectomy for relief of retinitis pigmentosa has been seriously considered by ophthalmologists. De Takáts and Gifford present the results of operation on six patients. In not one of the cases was there an increase in visual acuity or in the visual fields. One younger patient reported improvement in night blindness. In none of the cases was there progress in the disease, but the longest period of observation was only a year and a half. The authors believe that further studies on the effect of sympathectomy on dark adaptation and minimal light perception in these patients are indicated.

SPAETH, Philadelphia.

RÔLE OF MALARIA IN CONTROL OF ATROPHY OF THE OPTIC NERVE DUE TO SYPHILIS. C. P. CLARK, Arch. Ophth. **15**:250 (Feb.) 1936.

Clark presents a study of the cases of twelve patients with atrophy of the optic nerve due to syphilis who were treated with malaria. Eight of the patients had tabes, and two, dementia paralytica of the tabetic form. In eight instances there was improvement with therapy and in four no improvement. One of the eight patients was treated with intravenous injections of typhoid vaccine. In the four cases in which no improvement was shown the condition progressed until blindness resulted.

Clark believes that elevation of body temperature has received too much emphasis in the explanation of the effects of fever therapy. It has been pointed out that patients with dementia paralytica have shown improvement after undergoing an afebrile form of malaria. He believes that stimulation of the reticulo-endothelial system by the plasmodium produces increased resistance to the spirochete of syphilis. Additional factors, such as vasodilatation and increase in body metabolism, play a minor rôle in the defense developed against the spirochete after malaria.

SPAETH, Philadelphia.

USE OF BENZEDRINE FOR TREATMENT OF NARCOLEPSY. MYRON PRINZMETAL and WILFRED BLOOMBERG, J. A. M. A. **105**:2051 (Dec. 21) 1935.

Prinzmetal and Bloomberg selected nine patients with typical histories of narcolepsy for the study of the stimulating effect of benzedrine. In all instances the disease was well established, and the patients fell asleep at least three times a day. In seven instances cataplexy and other conditions associated with narcolepsy were present. Seven of the patients had been taking ephedrine in the usual therapeutic doses for a considerable period, but only one had obtained complete relief from the symptoms. Five noticed some improvement, and one, no improvement.

Of the nine patients treated four were hospitalized for more accurate control. Throughout the period of the experiment on these patients they were kept in ignorance of the medicine they were receiving and of the changes in the dosage, in order to rule out any psychic effect. Since both benzedrine and ephedrine, in aqueous solution, have a salty taste, the patients were given physiologic solution of sodium chloride by mouth at the regular time for medication when they were not taking either of the effective drugs. Careful records were kept. At the start of each experiment the patient was given physiologic solution of sodium chloride for a period of from three to seven days. Then for several days varying doses of benzedrine hydrochloride were administered, followed by equivalent doses of ephedrine sulfate for several days. Then, for a final period, benzedrine was again given. The dosage of benzedrine varied from 10 mg. once daily to 40 mg. three times a day, depending on the age of the patient and the severity of the disease. The five ambulatory patients could not be so carefully controlled, but with them also benzedrine and ephedrine were alternated, without their knowledge of the change. In all instances, complete relief from the attacks of sleep and practically complete relief from cataplexy resulted when suitable doses of benzedrine were given. This compound was approximately three times as effective as ephedrine. In four instances huge single doses of ephedrine, as high as from 80 to 150 mg., failed to give relief, while moderate doses of benzedrine, such as 30 mg., afforded complete relief from symptoms. In only one instance did ephedrine prove as effective as benzedrine; in no instance did it prove more effective. No diminution in the effectiveness of benzedrine has been observed as a result of its use over comparatively long periods. In several instances the patients complained that, although they did not fall asleep during the day, they also could not sleep at night. This was remedied by giving a smaller or no evening dose. There appears to be some individual variation in response to benzedrine. Therefore, it is best to start with small doses of 10 mg. and gradually increase the amount until the optimal effect is obtained.

EDITOR'S ABSTRACT.

A Case of Dercum's Disease and Its Treatment by Deep X-Rays. Stephen K. Montgomery, Brit. M. J. **1**:357 (Feb. 22) 1936.

The patient, a married woman aged 50, had suffered continuous and intense pain in the legs, which had been involved in a generalized obesity for the previous eighteen years. Since the birth of her first child twenty-nine years before there had always been some secretion in the breasts. Because some clinical features in the case suggested pituitary disturbance, irradiation of the pituitary was suggested on the basis of the recent work of Harris and Selinsky, suggesting pituitary involvement in Dercum's disease. The obesity resembled that of adiposogenitalis dystrophia. The result of high voltage roentgen irradiation was beyond expectation. The pain diminished after the second treatment and had almost disappeared. The improvement was maintained eight months after the therapy. The adiposity was not affected by the treatment.

Beck, Buffalo.

Ciliary (Migrainous) Neuralgia and Its Treatment. Wilfred Harris, Brit. M. J. **1**:457 (March 7) 1936.

Harris observed twenty-three patients with migrainous neuralgia, which he termed ciliary neuralgia. The age of incidence of the attacks varied from early childhood to old age. Pain occurred most commonly in the early hours after midnight, the paroxysms varying in duration from ten minutes to twenty-four hours. Migrainous neuralgia is a substitute form of migraine in which the pain is referred to the temple, eye, cheek and jaws. It is usually unilateral, though occasionally it may pass to the opposite side at the end of an attack. Nausea is frequent. On the other hand, cerebral phenomena, such as teichopsia, hemianopia, aphasia or monoplegia, never occur. This difference in symptoms may be due to vasomotor spasm of the middle meningeal artery instead of the posterior cerebral artery, as in migraine. Pain in migrainous neuralgia is referred along the recurrent meningeal branches of the trigeminal nerve. Such a view of its pathologic cause accounts for the beneficial effect produced in many cases of severe migrainous neuralgia by injection of alcohol into the supra-orbital or the infra-orbital nerve or into the inner two thirds of the gasserian ganglion, which produces a more lasting cure. In many cases the duration of the paroxysms may be as short as ten or fifteen minutes, sometimes from four to six attacks occurring in twenty-four hours. It is such brief attacks that might lead to confusion with tic of trigeminal origin. In certain cases of migrainous neuralgia the pain is referred especially into the eyeball and around the eye, and in a large proportion, nearly half, of the cases the eye becomes congested and lacrimose.

Beck, Buffalo.

Treatment of Myasthenia Gravis. Louis Minski and A. B. Stokes, Brit. M. J. **1**:1095 (May 30) 1936.

The normal transmission of excitation from motor nerve endings to the voluntary muscle fibers is concerned with the liberation of acetylcholine. In myasthenia gravis there may be insufficient liberation or increased destruction by choline esterase, or the threshold value may be altered by other factors, as Briscoe suggested. Feldberg and Vartiainen, working on the superior cervical ganglion of the cat, found that physostigmine strongly sensitizes the ganglion cells to injections of acetylcholine and that potassium ions have a similar but much slighter effect. Physostigmine was from sixteen to forty times more powerful than potassium in this respect. These considerations indicated the probable mode of action of physostigmine and di-methyl carbonic ester of 3-oxyphenyl-tri-methyl ammonium methylsulfate in myasthenia and also led Laurent and Walther to investigate the action of potassium chloride given by mouth. They found a demonstrable improvement with large doses of potassium chloride and a useful adjuvant action to di-methyl carbonic ester of 3-oxyphenyl-tri-methyl ammonium methylsulfate in small repeated doses.

Two young women were treated with this drug and with physostigmine and potassium chloride. It was concluded that the specific effect of di-methyl carbonic

ester of 3-oxyphenyl-tri-methyl ammonium methylsulfate in the treatment of myasthenia gravis is confirmed, but its value is considerably diminished by the toxic symptoms and the difficulties in its use outside a hospital. Potassium chloride appeared to have little adjuvant effect but considerably increased the toxic symptoms. Physostigmine in adequate doses produced apparent improvement, but with greater toxic effects.

BECK, Buffalo.

TREATMENT OF MYASTHENIA GRAVIS. HENRY J. WADE, Brit. M. J. **1**:1099 (May 30) 1936.

Two patients suffering from myasthenia gravis were treated with injections of the di-methyl carbonic ester of 3-oxyphenyl-tri-methyl ammonium methyl sulfate in an attempt to stabilize them rather than merely to alleviate the symptoms. This process meant daily injections of increasing amounts of the drug to the point at which no further improvement occurred. With certain doses atropine sulfate was injected, apparently to avoid severe toxic reactions. Both a concentrated and a standard solution were used. The results obtained in these two cases offer considerable encouragement for the continuous method of treatment for myasthenia gravis, and many interesting facts have been disclosed. No atropine was required in either case when the standard solution was used in doses up to 5 cc. three times a day, yet the use of the concentrated solution in equivalent doses produced severe abdominal pain. The motor action on the bowel of the concentrated solution appears to be greater than its effect on the myasthenic condition, whereas the standard solution, except in doses of 6 cc., had no effect on the bowel but a marked effect on the myasthenic condition. The administration of potassium chloride produced no effect in either case. The fact that the second patient required no atropine after the third day with 6 cc. of the standard solution favors the supposition of tolerance to this drug of some degree, but this was only demonstrable in its action on the bowel, for no such tolerance was demonstrated in over three months' observation of this patient's myasthenic condition.

The creatine and creatinine metabolism was not altered by the use of the drug. The injections produced no systemic disturbance and caused no inconvenience to the patients, and the psychologic improvement in their outlook was gratifying.

BECK, Buffalo.

THE TREATMENT OF TETANUS WITH CONTINUOUS AVERTIN ANAESTHESIA. LESLIE COLE, Lancet **2**:246 (Aug. 3) 1935.

Cole reports a case of tetanus in a child 6½ days of age. The cord, which separated on the fifth day after birth, was dressed with cotton wool and then with "rag." On the following day it was noticed that the child could not suck; the jaws seemed stiff, and the mouth could not be opened. Twelve hours later there were stiffness and spasms, and the symptoms became steadily worse. The baby was admitted to the hospital thirty-six hours after the onset of the illness, having had no food during that period. There was a purulent discharge from the umbilicus. Trismus and risus sardonicus were present, with complete inability to swallow fluids. Generalized reflex spasms of great severity, with opisthotonos, occurred every five minutes and lasted up to two minutes, involving particularly the muscles of the chest, abdomen and diaphragm so that respiration was completely stopped and cyanosis was extreme. The child was anesthetized with open ether and oxygen. A single dose of 100,000 international units of tetanus antitoxin was given intravenously through the anterior fontanel and 0.3 cc. of tri-bromethanol in amylene hydrate rectally. Eighty cubic centimeters of saline solution was administered subcutaneously. The umbilicus was cleansed with hydrogen peroxide, and hydrogen peroxide dressings were applied. A stomach tube was passed nasally and left in situ. The initial large dose of intravenous antitoxin was followed by continuous anesthesia with tribromethanol in amylene hydrate for eleven days and smaller doses for twelve days longer. Oxygen was given continuously through the nose

for long periods, and a normal diet was administered by stomach tube. A total of 19.2 cc. of tribromethanol was given in the first eleven days and 24.4 cc. altogether in twenty-three days.

Cole emphasizes the need for caution in administering tribromethanol, since the danger of large and repeated doses is not yet known. Parsons has shown that a dose of 0.475 Gm. per kilogram of body weight produced fatty degeneration of the liver in a rabbit; so the danger of toxic effects on the liver must not be overlooked. Some patients may have an idiosyncrasy to the drug. Boyd stated that children tolerate tribromethanol in ordinary doses particularly well. It is possible, however, that very large doses in adults may be more dangerous and less effective.

WATTS, Washington, D. C.

Diagnostic Methods

A MODIFIED TECHNIQUE FOR THE STEREOSCOPIC EXAMINATION OF THE SKULL BY X-RAY. Z. WILLIAM COLSON, New England J. Med. **213**:1067, 1935.

A method for the examination of the skull is described which avoids distortion. Two films are used, placed 30 inches (76 cm.) from the skull. The angles of the tubes are exactly the same as the angles made by the line of vision of the two eyes when the negatives are viewed in the stereoscope. Viewed as single plates the roentgenograms are useless, but in combination they present an image which is infinitely superior to those obtained with older methods. The principles of the method, described in detail, are in accord with Verhoeff's theory of binocular vision.

MOORE, Boston.

REACTIVE LEUKOPENIA AND ITS SIGNIFICANCE IN VARIOUS MENTAL DISEASES. ERIK GOLDKUHL, Acta psychiat. et neurol. **10**:1, 1935.

Goldkuhl reviews the literature concerning the variation in the leukocyte count of the blood in various physiologic conditions and mental diseases, with especial reference to leukopenia. He studied sixty-seven cases, ten of which were of normal conditions, ten of schizophrenia, ten of manic-depressive psychosis, twelve of constitutional asthenia, twenty-four of hysteria and four of posttraumatic psychoses. The results show that in normal persons, under the observance of proper conditions for research, reactive leukopenia does not occur. On the contrary, in the groups of patients with schizophrenia and manic-depressive psychosis such reactions occurred in a few instances. Of particular interest, however, is the fact that reactive leukopenia was observed in more than 50 per cent of the cases of constitutional asthenia and hysteria. The occurrence of leukopenia points to a general vegetative and psychic lability and represents a manifestation of a particular constitutional disposition.

YAKOVLEV, Palmer, Mass.

ATTEMPTS AT IMPREGNATION OF PROTOPLASMIC NEUROGLIA IN MASS ACCORDING TO THE METHOD OF LUGARO. R. GORDIN, Acta psychiat. et neurol. **10**:37, 1935.

From his experiments Gordin concludes that with the simple technic of Lugaro one easily obtains an elective impregnation of the protoplasmic macroglia in the cerebral cortex, cornua Ammonis and striatum. For material from other regions of the nervous system this method is not satisfactory. The method permits the use of the ordinary material fixed in formaldehyde; however, it is advantageous to prolong the fixation for a few days more, using a dilute solution of formaldehyde U. S. P. (9:50). The duration of fixation must not exceed two months, the optimum time being one and one-half months. When material older than one month is used only a concentrated solution of silver must be employed for impregnation. The method in its present form has the disadvantage of being limited to use for tissues from certain regions of the nervous system. Moreover, for a reason as yet

unknown, the impregnation is sometimes unequal in different areas of the section. However, these inconveniences are compensated for by the simplicity of the technic and the excellence of the microscopic pictures. YAKOVLEV, Palmer, Mass.

THE ARNETH BLOOD PICTURE IN DISSEMINATED ENCEPHALITIS AND DISSEMINATED SCLEROSIS. N. J. HANSEN and C. J. MUNCH-PETERSEN, Acta psychiat. et neurol. **10**:47, 1935.

Hansen and Munch-Petersen studied the Arneth blood picture in cases of disseminated encephalomyelitis and multiple sclerosis. The cases were classified into two groups on the basis of the clinical diagnosis prior to the examination of the blood. They found that in the cases designated as encephalomyelitis a distinct tendency to a shift to the left was shown in the Arneth blood picture, whereas in the cases typical of multiple sclerosis in their material a blood picture was shown which, according to the Arneth formula, came much nearer the normal condition. The authors believe that these findings support the view that there is an essential difference between the pathogenesis of multiple sclerosis and that of encephalomyelitis and that these findings argue against the infectious origin of multiple sclerosis. YAKOVLEV, Palmer, Mass.

ON THE PRACTICAL VALUE OF THE MYODYSTONIC REACTION IN THE EXAMINATION OF "NEUROSES." BENGT J. LINDBERG, Acta psychiat. et neurol. **10**:87, 1935.

Lindberg examined 250 patients with various organic and functional nervous disturbances; 214 had slight psychosis and various functional disturbances, 14 schizophrenia and the remaining 22 organic diseases of the nervous system (post-encephalitis, cerebrospinal syphilis, cerebral arteriosclerosis, trauma to the head, epilepsy, chronic myelitis and the like. The myodystonic reaction of Söderbergh (one or more after-contractions of the muscle following cessation of a tetanizing faradic current, instead of immediate and final relaxation) was positive in 15 cases of the total number. Ten of the cases in which the reaction was positive belonged to the group of organic disease, 3 to the group of schizophrenia, and 2 to the group of functional disturbance. Lindberg believes that his results lend support to the view that the positive myodystonic reaction indicates an organic change in the central nervous system and must be considered as a valuable aid in differentiation between organic and psychogenic conditions. Its relative frequency in cases of schizophrenia suggests the organic (extrapyramidal) nature of this mental disease.

YAKOVLEV, Palmer, Mass.

Society Transactions

DETROIT SOCIETY OF NEUROLOGY AND PSYCHIATRY

Regular Meeting, Jan. 9, 1936

LEO H. BARTEMEIER, M.D., *Presiding*

PERTINENCE OF PSYCHOANALYSIS. DR. T. K. GRUBER, Eloise, Mich.

In Hamlet Shakespeare discussed madness and summarized what is essentially the history and purpose of modern psychiatry as a need for the recognition of madness, the adoption of an attitude of pity toward it and the necessity for research as expressed in: "Now remains that we find out the cause of this effect."

Despite the long history of psychiatric thought, modern approaches date only from the latter part of the nineteenth century; not until then had there been sufficient development of the (so-called) basic sciences to permit other than descriptive or metaphysical approaches. The beginning of the present century was marked by the formulation of many significant concepts of psychiatric problems and by the initiation of new methods and approaches to the problems of mental disease. Kraepelin, in addition to evolving a system of classification, became the pioneer in experimental psychiatry and in 1892 contributed his classic study of the psychic effects of alcohol. Bleuler in 1910 expanded Kraepelin's original concept of dementia praecox and contributed greatly to an understanding of psychic symptomatology as a phenomenon in itself. Shortly before this, Adolf Meyer had presented his concepts of psychobiology, and Sigmund Freud had evolved a school of thought. For each of these contributors the paramount task in mind was the search for some explanation of the causal factors and relationships in mental disorders.

When one realizes that psychoanalysis is only forty years of age, it becomes apparent that no final decision concerning it can be offered, or even contemplated, at present. Further, psychoanalysis is the offspring of the two youngest of all sciences: psychology and psychiatry. Despite the fact that it has a longer history than any of the other sciences, psychology as a definite field of learning is not yet a hundred years old, and psychiatry as a science dates only from Kraepelin. Accordingly, in the light both of the slow development of the sciences in general and of its youth, psychoanalysis must be regarded as no more than an infant in arms. All that can be done at present is to evaluate its contributions to scientific thinking, understanding and practice.

The freudian theory is only an empiricism based on certain careful observations and compilations; it has been sponsored by enthusiastic supporters, and the charge is made repeatedly that it is a profitable cult and capitalizes successfully the fields once harvested by charlatans. However, concerning many of the freudian theories there can be no question of their contribution to the correlation of mental and physical processes.

Psychoanalysis has made a definite contribution to psychiatric thought. Psychodynamic concepts and theories of mental behavior, out of which there has developed a new and significant approach to the problems of human behavior, are examples. Out of these formulations have come the development of clinical psychology, the dynamic approach to psychiatric problems and the formulation of new and readily accepted concepts of mental disease. Adolf Meyer, who is antagonistic to many psychoanalytic teachings, readily concedes the value of many of the concepts and the close relationship existing between his psychobiologic formulations and the psychodynamic concepts of Freud, with which the whole body of psychiatric thought is permeated. One need only listen to a discussion of a psychiatric

problem to note the repeated and essential use of such terms as compensation, ambivalence, inferiority feelings, mental mechanisms, defense reaction, conversion symptoms, identification, regression, projection, psychic trauma and wishful thinking and innumerable other expressions which constitute a part of the accepted language of both orthodox psychiatry and orthodox psychoanalysis. Some of these terms belonged originally to nonanalytic thought; many of them were developed to meet the need for expression of concepts in psychoanalysis, but all, when scrutinized for their accepted psychiatric significance, are found to be endowed with meanings derived from the development of psychoanalytic thought or with significant or accepted connotations of psychoanalytic origin.

In other words, psychoanalysis has been a rich source of ideas and concepts for psychiatry in general. It is now recognized that seriously unpleasant psychic experiences may give rise to definite shock reactions, which are as significant as those arising from somatic injuries, but it was psychoanalysis that evolved the concept of a parallelism between psychic and somatic trauma. Even the bitterest critic of psychoanalysis speaks of the patient with catatonia regressing to the child's level of behavior, apparently unaware that the observation and recognition of regression to simpler levels of behavior are essentially one of the contributions of psychoanalysis to psychiatric thought. Similar observations may be made on every hand.

Still another contribution to psychiatry for which psychoanalysis must be given credit by virtue of priority has been the psychoanalytic teachings in regard to the value of the entire life history of the patient. Meyer, in his psychobiologic formulations, confirmed these teachings of Freud, first stressing the reality and situational aspects of the patient's life story and later emphasizing the interrelationships between psychic and somatic experiences. Freud and his followers, however, from the beginning emphasized the importance and need of an adequate history not only of the reality and situational adjustment of the patient but of the intellectual and emotional life as well. The concept of a life history strictly from the standpoint of psychic reality is peculiarly psychoanalytic and proves to be one of the most fertile concepts in modern psychiatry.

In brief, whatever may be the errors in theory, the misconceptions of its teachings, the misdirection, or even false applications, of its methods and the faults in its actual practice, psychoanalysis has contributed significantly to psychiatry by arousing interest in previously neglected aspects of human life, by developing the body of psychiatric thought and by evolving new approaches to psychiatric problems. For these reasons, at present one may say that psychoanalysis has demonstrated its pertinence.

Obviously, from what I have said, psychoanalysis is a rationalization or study of human behavior and misbehavior. For the neurosis and the so-called mild psychosis, psychoanalysis is a seeming solution. So far as definite psychoses are concerned its value is highly questionable, and despite many attempts to apply it to "organic" psychoses it has nothing to offer as regards the disease processes.

Psychoanalysis is a special branch of medicine, fraught with more dangers than the careless surgeon's knife or the narcotic needle. The sad admission must be made that the entire analytic set-up has been adopted by too many persons who call themselves psychiatrists and are able to memorize the jargon of psychoanalysis and speak of the psychoanalytic approach when, as a matter of fact, they would not know a psychoanalytic approach from a Filaria sanguinis hominis. Few persons are adapted by personality, integrity and mental endowment to practice this special branch of psychiatry, and unless more safeguards are placed around its practice, public legislation will be forced to take a hand in the situation. The vices and virtues are bound to become so mixed in the psychoanalytic approach to a neurosis that they may be difficult to straighten out. Only the most careful students of Freud who have been properly trained and have given the necessary amount of time to a personal analysis should be recognized by their confreres as capable of carrying on psychoanalysis. With proper background there can be no doubt that psychoanalysis is one of the greatest implements in the armamentarium of psychiatry.

NEW YORK NEUROLOGICAL SOCIETY

Regular Meeting, Feb. 4, 1936

ISRAEL S. WECHSLER, M.D., *President, in the Chair*

CEREBRAL COMPLICATIONS OF ICTERUS GRAVIS NEONATORUM. DR. SAMUEL BROCK and DR. ABNER WOLF.

In 1875 Orth first described a jaundiced condition of the basal ganglia and other nuclear masses of the brain as a complication of icterus in the new-born. In 1903 Schmorl gave the name *Kernikterus* to these lesions. There is little reference to this disease in neurologic literature; pediatric and medical journals have been the repository of most of the reports. Two important recent contributions have been made by Zimmerman and Yannet (Kernikterus: Jaundice of the Nuclear Masses of the Brain, *Am. J. Dis. Child.* **45**:740 [April] 1933; Cerebral Sequelae of Icterus Gravis Neonatorum and Their Relation to Kernikterus, ibid. **49**:418 [Feb.] 1935). Reference may be made to these articles for a complete survey of the literature. This cerebral complication is uncommon; Schmorl found 6 instances in 120 cases of fatal icterus neonatorum—an incidence of 5 per cent. It is not observed in adults or in association with obstructive jaundice.

The causes of icterus neonatorum will be discussed later. Children may be jaundiced or normal at birth; jaundice usually appears on from the first to the seventh day and becomes intense. In addition, the clinical picture is characterized by apathy, diarrhea, vomiting, drowsiness and collapse; nervous complications are frequent and consist of convulsions, spasticity, opisthotonos, irregular respiration and vasomotor symptoms. There is usually severe hyperchromic anemia, with many nucleated erythrocytes, poikilocytosis, basophilia and mild leukocytosis. The spinal fluid is yellow. Petechiae and ecchymoses often occur in the skin and mucous membranes. The liver may be slightly enlarged, and the spleen is usually considerably enlarged. More than 80 per cent of the children die during the first week of life, most of them on or before the fifth day. Others die after several weeks or may survive for months or years. One of the remarkable features of icterus gravis neonatorum is the tendency for the disease to appear in successive pregnancies, though the first one or two children may be spared. Hilgenberg reported 14 fatalities in a total of 22 pregnancies in 3 families. If the patient recovers signs of cerebral disease are likely to develop. Choreo-athetosis, spastic diplegia, mental deficiency, speech defect, hypotonia and emotional instability are the persistent sequelae. These evidences of severe and extensive involvement of the brain develop gradually in a child after a severe and almost fatal attack of neonatal icterus. It is probable that other siblings will have succumbed to the disease.

We shall present briefly a report of the history and pathologic changes in 3 cases of acute icterus and in 1 case in which there were chronic sequelae. The presumptive pathologic picture in the chronic type is based on studies in other cases.

At the Babies Hospital and the Sloane Hospital for Women 3 cases of acute icterus of the new-born were encountered in 2 boys and 1 girl. The family histories were negative for this disease. All the children were full term. One of the boys was deeply jaundiced at birth, had a large liver and spleen and exhibited subcutaneous ecchymoses; there was associated erythroblastosis. Respirations were irregular, and he soon lapsed into stupor and died at the beginning of the third day after birth. The other boy became icteric a few hours after birth, took food poorly and was flaccid; his cry was feeble. The liver was somewhat enlarged, and respiration was irregular. He died on the second day. The girl seemed normal until the third day, when icterus developed, with a similar clinical picture; she died in twenty-four hours.

The chronic residua are illustrated in the case of J. B., a boy aged 6¾ years. The mother said that he had had jaundice when he was 6 years old. The father died after five months in a state hospital, in February 1936; he had been regarded as suffering from a paranoid type of schizophrenia. There had been 5 pregnancies; the first 2 were uneventful, and the 2 healthy boys were 15 and 13 years of age. In the third pregnancy a girl was born; jaundice developed, and she died in four days. The fourth pregnancy resulted in a stillbirth at the eighth month. The patient had jaundice at the age of 3 days and was very ill for six weeks. The mother noticed that his head "wobbled" afterward. He had pneumonia at 11 months. He did not sit up until the age of 14 months and could not walk until he was 2½ years old. The mother noted that the gait was abnormal, that he was backward mentally and that he dribbled saliva. At the time of examination he presented a clinical picture of double athetosis. The head was not held erect; saliva drooled from the mouth; speech was slow and drawling, and he made facial grimaces. The upper extremities, especially the hands, showed purposeless involuntary twisting movements; they were more evident on the left side. The same movements were seen in the lower extremities to a less degree. The pupils were equal and reacted well. The optic disks were normal. There was restricted movement of the eyes in downward gaze. The deep reflexes were present. A Babinski toe sign was elicited on the left. There was a considerable degree of intellectual impairment. There had been no disorders of conduct and no disturbances in the emotional sphere. The liver was not palpable.

The pathologic changes in this condition may be divided into the acute and the chronic stages, corresponding to the similar phases of the clinical syndrome. In the acute condition, with death soon after birth, the observations at autopsy are: jaundice of all organs; slight enlargement of the liver and often considerable enlargement of the spleen; deep red bone marrow and frequent evidence of hematopoiesis, chiefly of the erythroblastic type, in the liver and spleen. In only a few cases damage of the liver cells is shown. Bile thrombi are frequent in the bile canaliculi of the liver, and a great deal of bile pigment is present in the liver cells. There is often hemosiderin in the spleen and liver. There are usually jaundice and edema of the leptomeninges and choroid plexuses. The caudate nucleus, putamen, globus pallidus, thalamus, corpus Luysi, mamillary body, cornu ammonis, red nucleus, nuclei of the cranial nerves, olives and dentate nucleus, as well as the anterior and posterior horns of the spinal cord, are usually intensely icteric. The cerebral and the cerebellar cortex, as well as the cerebral white matter, have also been observed to be jaundiced in some cases.

In each of the 3 cases of the acute stage in our series there was severe generalized icterus, with jaundice of the central nervous system, which involved especially the basal ganglia and nuclei of the cranial nerves. The globus pallidus was more intensely stained in the girl, and the central white matter of the right cerebral hemisphere, in the shorter-lived of the boys. The anterior and posterior horns of the spinal cord were involved in 2 instances.

On microscopic examination one observed nerve cells in the affected nuclear masses showing varying degrees of degeneration and intensity of icteric pigmentation. The pigment in the cells was homogeneous. The icteric cells lay among comparatively normal or partly degenerated, unpigmented cells. The interstitial tissue contained fine and coarse granules of pigment but no crystals. These often appeared to be in dendrites and perhaps in axons; occasionally they also occupied a polar position in relation to microglia nuclei. On the whole pigmented nerve cells were not observed frequently. It was more common to see a diffuse yellowish discoloration of the interstitial tissue, as in the inferior olive. Frequently grossly pigmented areas showed no discoloration microscopically; this observation has been made by previous investigators, and the absence of pigment is probably caused by undue lability of the pigment involved. In the white matter the pigment probably lay in myelin sheaths—an observation which accords with the fact that bile pigments have a definite affinity for lipoids. There was no evidence of any definite glial, mesenchymal or inflammatory reaction.

There have been various theories as to the origin of icterus neonatorum gravis. Pfannenstiel and others have attributed it to a congenital dysfunction of the hematopoietic and bile-forming systems. Huwer expressed the belief that there was an abnormality in the detoxifying power of the liver. A third theory, sponsored by Hoffmann and Hausmann, postulated maternal toxemia. Beneke and Esch were the chief exponents of the theory of neonatal sepsis; Zimmerman and Yannet were inclined to agree with this view. The last explanation, however, does not adequately cover the group of familial forms and especially those in which there is erythroblastosis. It may be that different etiologic factors produce identical pathologic lesions, which give rise to similar clinical pictures. Difficult labor and prematurity are apparently of no significance.

The majority of investigators who have studied kernicterus agree that degenerative changes in the nerve cells occur first and that the injured elements then become bile stained. A few have held that the bile pigments first injure and then impregnate the ganglion cells. This is not incompatible with the fact that no similar condition occurs in adult obstructive jaundice, for there is evidence that the bilirubin observed in kernicterus is not quite like that seen in ordinary jaundice. It may be that the same toxic process, whether it is sepsis or a congenital defect in the detoxifying power of the liver, produces the hemolysis, anemia and jaundice, as well as the degenerative changes in the brain. On the other hand, the striking involvement of the basal ganglia naturally brings up the question of a primary hepatic process, especially in view of the experimental work of Weil and many others and of the cases grouped under the head of hepatolenticular degeneration. It is true, however, that in very few cases of kernicterus has any degeneration of the hepatic cells been shown. The occurrence of this condition in only 5 per cent of cases of icterus gravis is also difficult to explain.

The pathologic changes in the chronic form have been studied in only 3 instances. Cases of the late stages were described by de Lange, Burghard and Schleussing and Zimmerman and Yannet. In general, chronic degenerative lesions were described in the areas which showed acute degeneration and pigmentation in the acute form. In the case of Burghard and Schleussing, in which the child died at the age of 5 months, there was marked loss of ganglion cells in the nucleus caudatus, globus pallidus and putamen, with moderate gliosis. There was widespread loss of myelinated fibers in the globus pallidus. The subthalamic nucleus also showed considerable demyelinization and gliosis. The patient observed by Zimmerman and Yannet lived till the age of 3 years. They observed destruction of many nerve cells in the caudate nucleus, putamen, cornu ammonis, substantia nigra and dentate, lateral, thalamic and red nuclei bilaterally; the cells and medullated fibers of the pallidum were destroyed. There was periventricular demyelinization about the posterior horns of the lateral ventricles and in the lateral columns of the cord.

DISCUSSION

Dr. Richard Brickner: Was there any study of the lesions in the white matter?

Dr. Abner Wolf: In case 1, in the boy who lived about eight days, there was intense icteric pigmentation of the white matter of one cerebral hemisphere.

Dr. Richard Brickner: Not in the gray matter?

Dr. Abner Wolf: Yes, there was the usual involvement of the gray matter.

Dr. Charles Davison: About three years ago I saw a child suffering from Cooley's erythroblastic anemia and jaundice. During his stay in the hospital parkinsonism developed. Histopathologically the changes were similar to those in the case described by Zimmerman and Yannet, as shown by Dr. Brock and Dr. Wolf. There was demyelinization of the globus pallidus, and typical Alzheimer cells were noted, comparable to those seen in Wilson's disease. On sectioning the brain my colleagues and I did not observe the intense yellow pigmentation seen in kernicterus. I wonder whether the icteric tint in the brain existed early in the course of the disease. In the chronic stage of the disease a glial reaction

may take place. I wish to ask Dr. Brock and Dr. Wolf whether a glial reaction and Alzheimer glia cells were observed in their cases. I suspect that they were, for in one of the slides of the acoustic nucleus which they showed there were, I thought, large, pale glia cells. Am I misinterpreting the slide?

I wish to know the explanation for the dropping out of the ganglion cells in the hippocampus. Was this due to the jaundice or to ischemia arising from vascular spasm or obstruction?

DR. GEORGE H. HYSLOP: Dr. Brock and Dr. Wolf have called attention to the fact that severe icterus may affect the basal ganglia. I wonder if they have given consideration to the reverse side of the picture, namely, the frequency with which children exhibiting various forms of disease of the basal ganglia and other degenerative cerebral diseases have had a history of severe icterus in early infancy.

DR. ABNER WOLF: From Dr. Davison's description, I believe that his case was one of kernicterus at birth, for the literature contains the reports of about 6 cases of erythroblastosis, with severe jaundice at birth, in which there were kernicterus and the characteristic microscopic observations. The degeneration of the cells of the cornu ammonis is, I believe, due to whatever brought about the degeneration of the cells elsewhere, for the explanation of which there are many theories. It may be that there is a poisonous protein fraction at work, produced by impairment of hepatic detoxifying power. The jaundice may be of hepatic origin and the cells secondarily pigmented. On the other hand, it may be that the jaundice is primary and that the pigment lies about the cells, disturbs their function, causes necrosis and then stains them secondarily. I did not observe any hypertrophied astrocytes resembling Alzheimer glia cells in the affected areas.

In answer to Dr. Hyslop's question: Dr. Walter Klingman, at the New York Neurological Institute, has studied a large series of cases of so-called Little's disease; he gathered 40 cases in which there was, according to his criteria, severe icterus at the time of birth or shortly after. He reviewed these criteria with a group of pediatricians, who expressed the belief that icterus was severe enough to be differentiated from icterus simplex, i. e., the ordinary icterus neonatorum which occurs in a large number of children at birth. He will report this series of cases shortly in the *Bulletin of the Neurological Institute of New York.*

DR. JOSHUA ROSETT: Did the bile salts stain the nerve tissue in a selective way?

DR. ABNER WOLF: One occasionally finds bile-stained cerebrospinal fluid in cases of obstructive jaundice of adults, but one does not observe kernicterus.

DR. JOSHUA ROSETT: I mean, in experimental tissue.

DR. ABNER WOLF: No, staining of the nerve tissue with bile salts has never been produced experimentally. We attempted to tie off the common bile duct in rabbits and produce icterus and then secondarily tried to produce degeneration of the basal ganglia of the rabbits by carbon monoxide poisoning, but it was difficult to keep the animals alive.

DR. JOSHUA ROSETT: Have you tried to stain normal sections with bile salts?

DR. ABNER WOLF: No. The bilirubin encountered in this condition seems to be a different kind from that found in ordinary obstructive jaundice. The stained organ does not turn green when placed in formaldehyde, as in a case of ordinary jaundice, but remains yellow. One must treat the sections containing the pigment with potassium hydroxide before one can obtain a positive Gmelin test.

DR. HENRY ALSOP RILEY: I wish to ask Dr. Wolf if he thinks there is any possibility that the structures which show almost selective absorption of the bile pigment do so because of being bathed in a considerable amount of cerebrospinal fluid. The appearance suggests to me that the meninges and the structures in the midbrain, as well as the nuclei superficially placed in the brain stem, are stained. These structures are exposed to large quantities of bile-containing fluid. Is it possible that the coloration may be due merely to absorption of the bile salts by the gray matter in rather close relation to the spinal fluid?

Dr. Lawrence S. Kubie: In interpreting the significance of the staining with bile pigment it is difficult to eliminate the possibility of postmortem diffusion. It is known that cell membranes are often permeable to substances after death or injury to which they are impermeable in life or before injury. The changes described and illustrated in the lantern slides showed in some instances that the cells had undergone destructive alterations before death. Such cells could certainly, or at least conceivably, take up pigments. On the other hand, there were other cells which looked normal but which were diffusely stained. Furthermore, there were other areas, as in the olives, in which all the tissues were stained diffusely in broad bands. Since there must be an accumulation of bile pigment in the cerebrospinal fluid that bathes the surfaces, it is at least conceivable that much of this staining occurred as postmortem diffusion at the moment of death or soon after.

Dr. Wolf has pointed out that the bile pigment may not itself be injurious and has cited the suggestion of some one that the damage may be brought about by a protein fraction. To this consideration it might be well to add that wherever there are bile pigments one must also look for bile salts and bile acids; their effects may be even more significant in this connection.

Dr. Abner Wolf: I think it is possible that what Dr. Riley suggested may be true, but I believe that the pigmented areas have probably first undergone degeneration. Vital dyes are likely to impregnate areas which are degenerated and not to stain those that are more nearly normal.

I agree with Dr. Kubie that the bile pigment may not have caused the original degeneration of the cells but may only secondarily have pigmented the cells which were undergoing degeneration. It may act as a vital stain of cells which have already undergone necrosis.

Astereognosis in Association with Tumors in the Region of the Foramen Magnum. Dr. Joseph E. Rubinstein (by invitation).

Tumors in the region of the foramen magnum may give as their only focal signs and symptoms sensory changes, the most striking of which is unilateral astereognosis. The sensory disturbances in cases of tumor of this region are practically the same as those in lesions of the cortex of the parietal lobe; patients with a tumor of the foramen are, therefore, usually believed to be suffering from a cerebral lesion contralateral to the hand in which astereognosis appears. They are often subjected to unnecessary cerebral craniotomy. This is illustrated by the following 2 cases.

Case 1.—A man aged 58 was admitted to the Montefiore Hospital in June 1933, with complaints of severe headache, pain in the suboccipital region and numbness of the left hand for five months. Examination revealed stiffness of the neck and complete astereognosis on the left side, with slightly diminished position sensibility and two point discrimination in the left hand. There was full preservation of the primary qualities of sensation—touch, pain, heat and cold. Several examinations of the spinal fluid gave normal results. Roentgenograms of the cervical portion of the spine showed spondylitis, to which the stiffness of the neck was attributed. An encephalogram had shown excessive accumulation of air in the subarachnoid space, especially over the right cerebral hemisphere, but no air in the ventricles (May 1933). The diagnosis was vascular encephalopathy, with a focal lesion in the right parietal lobe. The left upper extremity became progressively weaker, and shortly before the patient's death, three weeks after his admission, astereognosis developed also in the right hand. Postmortem examination disclosed a meningioma in the foramen magnum, compressing the medulla oblongata and upper cervical portion of the cord.

Case 2.—A man aged 29 was admitted to the Barnes Hospital, St. Louis, in September 1934, with the complaint of headache in the right frontal region and vomiting of five months' duration. Two weeks before his admission there developed blurring of vision and symptoms in the left hand suggesting astereognosis. Examination showed marked bilateral papilledema, with large superficial hemor-

rhages in the fundi, and complete loss of recognition of the form, texture and shape of any object in the left hand. Power in both hands, measured with a dynamometer, was normal, and careful sensory examination showed that the elementary sensations were intact. There were only slight impairment of position sense (evidenced only by pseudo-athetosis) in the fingers of the left hand and diminution of two point discrimination (indicated by the compass test) on the left side. The clinical diagnosis of tumor of the right parietal lobe was made. On exploratory cerebral craniotomy no evidence of tumor in that region was observed. Subsequent ventriculography showed symmetrical dilatation of the ventricular system. Suboccipital cerebellar craniotomy was finally performed, and a midline cerebellar hemangioblastoma extending into the upper cervical portion of the canal was removed.

Only 6 similar cases were found in the literature. In 4 of these extramedullary and in 2 intramedullary tumors of the uppermost cervical portion of the cord and the lower portion of the medulla oblongata was present.

The sensory deficit in all these cases was more or less identical with that resulting from a cortical lesion of the parietal lobe. According to Head, Dejerine, Oppenheim and others, astereognosis due to a lesion of the parietal lobe is practically always accompanied by some loss of position sense and two point discrimination in the affected hand.

The tentative explanation of these sensory disturbances is that the growth causes a lesion of the uppermost cervical portion of the cord or of the medulla oblongata; if the lesion is higher in the medulla, the posterior columns, the nucleus gracilis and the nucleus cuneatus or the medial lemnisci are affected by direct pressure or by interference with the vascular supply. In each of the 6 cases of extramedullary tumor the growth was situated on the posterior or posterolateral surface of the upper cervical part of the canal.

In cases in which general symptoms of intracranial pressure are present, ventriculography should be made to localize the lesion responsible for the astereognosis.

DISCUSSION

DR. LEO M. DAVIDOFF: Dr. Rubinstein has called attention to, if not a common, at least an important observation. I think he has confined his discussion to tumors extending through the foramen magnum not because the symptom of astereognosis occurs exclusively in cases of these lesions. I believe that extension through the foramen magnum is not necessary and that a tumor occurring in the upper cervical region may produce the same symptom. In my own experience 2 cases have occurred in which this symptom was presented; the lesion proved to be in the upper cervical region, without extension into the foramen magnum. In both cases a lesion of the parietal lobe was suspected. One was the case of a boy aged 19 years, who was seen by a neurologist at a time when the only symptom was astereognosis in the left hand. By the time I saw him there were pyramidal tract signs in both lower extremities. After a roentgenogram of the cervical region showed fractured vertebrae he confessed that he had been playing football and was trying to keep this information from his family. The symptoms progressed rapidly. A manometric test of the spinal fluid gave normal results; so no operation was performed. The symptoms gradually disappeared. The nature of the lesion was not known, but its location was undoubtedly in the upper cervical region.

The second patient presented himself with the same symptoms, and I suspected a lesion of the parietal lobe. A month had intervened between the time when I first saw him and his admission to the hospital, when similar signs were present in the other hand. This led me to believe he might have a lesion of the cervical part of the cord, and roentgenograms showed destruction of bone in the second and third cervical vertebrae. Exploration in this region revealed a perineurial fibroblastoma. In this case the upper pole of the tumor was definitely caudad to the foramen magnum. One ought to be extremely careful in accepting astereognosis as a sign of lesion of the parietal lobe; if no other signs are present one should

examine the cervical portion of the spine as well as perform air studies. This is particularly true if the patient with astereognosis shows no signs of involvement of the pyramidal pathways above the cervical region, that is, no central facial paresis. In the presence of central facial weakness, which practically always occurs in case of a tumor in the parietal lobe, a lesion high in the cervical portion of the cord is definitely ruled out.

DR. HENRY ALSOP RILEY: This is an important presentation, for I believe that if neurologists continue to think loosely in these terms mistakes of this kind will be made, with consequent unnecessary or misplaced operations and probably much damage to the patient. I believe that the term astereognosis is improperly used in this connection and should be reserved for clinical conditions in which the patient is unable to recognize the form of objects, in the presence of intact primary sense qualities. The senses of movement, vibration, touch, pain and temperature are all primary sense qualities. Any one of these may be interfered with at any point from the primary receptor in the skin to the terminal end-stations in the central nervous system. Any one, if interfered with, may or will produce inability to recognize objects by palpation. If one has an anesthetic hand one cannot recognize by palpation alone objects taken into that hand. If one has loss, or even moderate or inconsiderable diminution, of muscle tendon sensibility one cannot recognize objects by palpation alone. If the primary sense qualities are intact or practically normal the inability to recognize objects by means of palpation alone means interference with the synthesizing function of the parietal lobe, and the use of the term astereognosis should be confined to this loss of associative power and should not be applied to conditions in which the inability to recognize objects is the result of reduction or absence of the simpler constituents contributing to this synthesis. If anything is known about the functions of the parietal lobe, and this applies particularly to the superior parietal lobule, it is that the function of this region of the brain is primarily for the synthesis of primary sense qualities into more complex conceptions.

I believe that all the authors cited by Dr. Rubinstein fell into the same error, namely, that of applying the term astereognosis to a disturbance predominantly in one or another of the primary sense qualities. In these instances the patient was unable to recognize objects held in the hand by reason of deficiencies in the primary sense qualities and not of actual loss of ability to synthesize and elaborate these simpler qualities into more complex associations. In all the instances cited the lesions were so located as to produce direct or indirect pressure on the medullary nuclei or the tracts of the spinal cord. This pressure in all cases reported resulted in interference with primary sense qualities. The feature which caught the examiner's eye was the inability to recognize objects rather than the reduction of the primary sense qualities; as a result, the situations were reported as astereognosis, whereas they should have been recognized as disturbances in the conduction of the primary sense qualities.

Errors in diagnosis and incorrect operative procedures may be avoided by more careful thinking and more accurate examination. The inability to recognize objects may occur from interference with primary sense qualities or the synthesis of these simpler factors into more complex associations by the parietal lobe. The restriction of the term astereognosis to conditions in which there is inability to recognize objects by palpation alone, where primary sense qualities are intact or nearly so, will clarify the situation and reduce the number of incorrect diagnoses and inappropriate operations.

DR. JOSEPH E. RUBENSTEIN: In reply to Dr. Riley I wish to mention that Henry Head, who studied an extensive number of small discrete injuries to the parietal lobe, found that in most of the cases when there was astereognosis there were also defects in position sense and two point discrimination. In my cases I was careful to mention that the primary sense qualities of touch, heat, cold and pain were intact.

DR. JOSHUA ROSETT: May I ask Dr. Riley if astereognosis ever occurs in the presence of intact position sense?

DR. H. A. RILEY: I believe that position sense is a different faculty. I think that position sense is a combined synthetic gnostic sense quality, whereas the sensation of movement is a primary sense quality and is quite different in essence.

DR. GEORGE H. HYSLOP: To go back to etymology: Astereognosis means inability to know position in space and implies a defect in tactile space perception. Without his having said so, I think that Dr. Rubenstein associates the word with the cortex and assumes that such localization is implied. Actually, astereognosis implies either receptive or perceptive dysfunction and, accordingly, is associated with lesions below, as well as at, the cortical level.

DR. H. A. RILEY: I wish to call Dr. Hyslop's attention to the fact that astereognosis means the ability to recognize form.

DR. GEORGE H. HYSLOP: Form sense and position sense are, in a manner, the same. Without position sense one cannot perceive form. Dr. Riley is correct, however, as to the literal meaning of the word.

THE THALAMUS IN RELATION TO THE CEREBRAL CORTEX. DR. ARTHUR EARL WALKER, New Haven, Conn. (by invitation).

The thalamus may be divided into three groups of nuclei. The first includes nuclei having entirely subcortical connections and concerned either with a phylogenetically old system (the nuclei of the midline and the nucleus ventralis anterior) or, probably, with intrathalamic associations (the intralaminar nuclei). The second group (the nucleus ventralis lateralis, the nucleus ventralis posterior, the anterior nuclei and the geniculate bodies) consists of the nuclei receiving fibers from the ascending sensory tracts; the impulses are then sent to the cerebral cortex. The third group (the nucleus medialis dorsalis, the nucleus lateralis and the pulvinar) receives no fibers from the great ascending pathways but has numerous connections with the thalamic nuclei of the second group and sends fibers to the association areas (Flechsig) of the cerebral cortex, whereas the fibers of the second group end in the projection areas. In the nuclei of the third group there is probably some integration of the afferent impulses before they are relayed to the cerebral cortex.

DISCUSSION

DR. HENRY A. RILEY: I am much interested in the paper of Dr. Walker's, for I have been toiling lately with the nomenclature of the thalamus in man. I wish to ask Dr. Walker how analogous he believes these primate nuclear groups are to the groups one finds in man and whether the terms can be used with equal applicability in the human and the primate thalamus. A second question concerns the anterior disseminate thalamic nucleus. Some time ago I had occasion to reconstruct the thalamic nuclei in the majority of the primate group; one of the interesting features was the emergence of the anterior disseminate nucleus, beginning in the gorilla, becoming larger in the chimpanzee and reaching its acme in man. So far as I know it does not appear in orders below the gorilla, although I am not sure about the orang. As I compared the reconstructions it seemed to me that this nucleus appeared and grew in relation to the expansion of the prefrontal area. This is the only area which is not represented to any extent below the gorilla. I wish to ask if Dr. Walker has any information in regard to the connection of the disseminate thalamic nucleus with the prefrontal region.

DR. CHARLES DAVISON: I wish to ask Dr. Walker about the nature of the lesions made in these animals. How can one tell whether the degeneration of the nerve cells of the thalamus was due to the original lesion or to distant effects? If I am not mistaken, some of these lesions were fairly extensive, and surely other areas must have been implicated.

DR. A. EARL WALKER: In answer to Dr. Riley's question regarding the analogies of the thalamic nuclei of the monkey and man: In general one can

carry over the nomenclature from the monkey to man. It is true that certain of the nuclei are much more developed in man than in the monkey, but they are all present in the monkey. No new elements are added.

In regard to the anterior disseminate group, in monkeys there is a small nucleus located dorsolaterally to the nucleus medialis dorsalis which corresponds to this group in the higher primates. It does not degenerate in cortical lesions, and I believe its function concerns intrathalamic associations.

In reply to Dr. Davison: The lesions which were made in this study were carried out under aseptic technic a large or small area of the cortex being extirpated with the Bovie unit and blunt dissection, as warranted. In each instance the extent of the lesion in the cortex was shown, so that the amount of damage to the white matter lying just under the cortex could be accurately assessed. However, if there were distant effects from these lesions due to interruption of the thalamic blood supply one would assume that the same thalamic damage would occur whether the lesion were in front of or behind the central fissure, as in each instance the vessels of the central sulcus would be involved. Quite different areas of degeneration, however, are observed in the thalamus after such lesions. Moreover, vascular disturbances in the thalamus produce histologic pictures quite different from those seen as the result of such cortical lesions. The latter produce true retrograde cellular degeneration.

SERIES OF CASES OF SEROUS MENINGITIS. DR. LEO M. DAVIDOFF and DR. CORNELIUS G. DYKE (by invitation).

Symonds recently called attention to a condition which he called otitic hydrocephalus. It has been referred to in the literature more or less sporadically since the beginning of the second half of the nineteenth century. This condition in its typical form consists of signs of increased intracranial pressure, headache and papilledema. There is no fever. The cerebrospinal fluid is clear and under markedly increased pressure, but its constituents are normal.

It is my purpose in this communication to crystallize further the conception of this disease, to present additional aids in diagnosis and to suggest some modes of therapy which have proved successful in the majority of cases in this series. The report is based on 15 cases observed at the Neurological Institute of New York during the past five years. The patients were all relatively young, the oldest being 43 and the youngest 4½ years, with the majority under 30 years. Eleven patients were females and 4 males. A history of otitis media occurred in 4 cases; in 2 other instances there was a history of infection elsewhere in the body some time before the onset of the present illness.

Symptoms.—In practically all cases the outstanding symptoms were headache and failing vision. The duration of the symptoms was surprisingly short. In only 2 patients had the illness lasted for two years prior to admission to the hospital. One patient noted failing vision fifteen months before admission. In all others the duration of the disease was six months or less, the shortest being twelve days.

Neurologic Examination.—The chief sign in all cases was papilledema, often of a high degree (from 3 to 6 diopters); in no case was there less than 2 diopters of swelling. In 10 cases there were practically no other neurologic signs, except for diminished visual acuity. In the remaining cases such signs as were present were referable to the pyramidal system and were of slight degree. They consisted of a slight exaggeration of reflexes, mild central facial paresis and a positive Babinski sign. In addition to these signs, there was some ataxia in 2 cases.

Examination of the Spinal Fluid.—The spinal fluid showed a normal cell count in all but 1 case, in which 66 cells were present. The amount of total protein was normal, except in 1 instance in which there was 75 mg. per hundred cubic centimeters. Tests for globulin gave negative reactions except one plus in the case in which the high cell count occurred. The colloidal gold curve was normal and the Wassermann reaction of the spinal fluid was negative in all instances. One patient had a Wassermann reaction of the blood of four plus.

Roentgenograms of the Skull.—Plain films of the skull showed evidence of increased intracranial pressure in 10 cases. In 5 cases evidence of chronic infection of the mastoid was revealed; in 2 of these instances no history of otitis was given, whereas in 1 case of otitis the mastoids were normal on roentgenography. In all but 2 cases pneumo-encephalograms were made. In 1 of the remaining cases normal ventricles were shown by ventricular estimation. In 12 of the 14 cases in which air studies were made ventriculograms were also made. In 6 cases ventriculography proved unsatisfactory and was followed by encephalography. In 2 instances encephalography alone was done. The reason for the primary injection of air directly into the ventricles was, of course, the presence of papilledema. The evidence obtained from the study of the pneumoroentgenograms was uniformly that of a ventricular system of normal size, shape and position.

A number of interesting points arose in association with these air studies: First, the fact that in so high a percentage of instances direct ventriculography failed to show satisfactory filling, is to be explained by the small size of the ventricles and the high intracranial pressure. We believe that these two phenomena caused expulsion of the gas along the needle track. As evidence of this we often observed filling of the cerebral sulci and subarachnoid cisterns with gas primarily introduced into the ventricles but escaping to these locations.

Treatment.—Thirteen of the 15 patients were treated with subtemporal decompression. One, a child with some ataxia on clinical examination, had a suboccipital exploration and decompression, and the other had no operation. In addition, the patients were treated with dehydration measures, consisting of limitation of fluid intake, saline cathartics or retention enemas and hypertonic dextrose solution when indicated.

Results of Therapy.—All patients improved during their stay in the hospital. This was evidenced by the disappearance of headache, partial recession of the edema of the optic disk and improvement or arrest of the failing vision. After leaving the hospital they were followed for periods varying from a few months to several years. The dehydration measures were continued at home, and improvement continued after discharge, but final disappearance of the papilledema required from six months to several years. There was occasional recurrence of headache, which was never severe.

One patient, three months after discharge from the hospital, died of another condition, while at home. The brain was obtained; examination, as in many cases reported in the literature, showed no indication of inflammatory disease. Pericellular and perivascular spaces were observed, which one may interpret as due to edema, but the explanation is uncertain, since the fixation of the specimen was not perfect and the spaces may have represented postmortem shrinkage.

Comment.—One of the most difficult problems associated with this syndrome is to find an appropriate name to describe it. Serous meningitis, applied tentatively by us, is obviously unsatisfactory, since clearly one is not dealing with an inflammatory disease, unless it is a sympathetic response of the choroid plexuses to inflammation elsewhere in the body. The name otitic hydrocephalus, recently proposed by Symonds, is inept for two reasons: First, in the majority of cases in our series there was no history or other evidence of otitis media and, second, air studies, which Symonds did not make in his 3 cases, showed no evidence of hydrocephalus, unless one might call the excess of fluid in the subarachnoid spaces external hydrocephalus.

In the examination it seems to us that in none of these cases can a tumor or other localized disease, such as adhesive arachnoiditis, be excluded without pneumoencephalography. The characteristics to be noted in the examination of the pneumo-encephalograms are: a normal ventricular system as regards size, shape and position; difficulty in filling the ventricles by ventriculography, and the escape of gas during ventriculography into the subarachnoid cisterns and sulci.

In the treatment of these patients, we believe that subtemporal decompression, while not essential, is important. This is especially true if the elevation of the

optic disks is great and the patient's vision is imminently threatened. With decompression reduction in the intracranial tension is at once brought about. This, however, does not prove to be adequate, and further reduction in pressure can be accomplished by repeated lumbar punctures and the dehydration methods already described. In the further treatment the decompression also plays an important rôle, since the degree of bulging and tension of the area of decompression acts as a barometer for the state of intracranial tension and thus serves as a guide for other therapy.

The prognosis is uniformly good, although cure does not come about rapidly. It is our impression that it takes many months, or even years, before a normal equilibrium between the production and the absorption of the cerebrospinal fluid is established.

DISCUSSION

Dr. Henry Alsop Riley: I am much interested because my associates and I have seen a number of cases of the same nature at the New York Neurological Institute, and I think all appreciate the difficulties in differential diagnosis of this condition and the picture presented by neoplasms which may develop in silent areas. Perhaps neurologists are in an unfortunate position in this situation, since they have some one to whom they can "pass the buck"—in other words, the neurosurgeon. After the neurologist has finished his study in these cases and can go no further, he has the neurosurgeon to whom he can turn and say: "I have done all I can, and now let's see what you can do." If neurologists did not have this facility of transmission in these cases, perhaps they might be forced to more intensive diagnostic thought in regard to this condition and might try to handle it themselves. It seems to me that if in the management of the situation one had the courage to do repeated lumbar punctures and remove enough fluid a result could be obtained as satisfactory as that obtained by decompression, and perhaps more beneficial in the end. After one has removed a portion of the cranium by decompression not much more elasticity is provided to the intracranial cavity, as there is a definite limit to which the dura can be stretched. The difficulty is in having the courage to do a lumbar puncture when one thinks one may be dealing with a silent cerebellar neoplasm; perhaps puncture should be reserved until after the important diagnostic criteria are obtained, preferably, I presume, by ventriculography. It seems to me that after this has been done and one finds a normal ventricular system, instead of performing a decompression, it would be as satisfactory to treat the patient with repeated lumbar punctures. One can perhaps assume that in the presence of an unaltered and undilated ventricular system one is not dealing with a tumor of the posterior fossa.

The other point which interested me was the question of nomenclature. First, it seems to me that the term meningitis is incorrect, and I think it is time that neurologists had courage to devise another term for disturbances in the meninges which are not the result of inflammation. Perhaps the word meningopathy might be used in this connection, although it has an unpleasant sound, just as encephalopathy and myopathy are used to designate two similar processes.

It is essential to determine whether the accumulation of fluid is due to interference with the process of absorption and under these circumstances might correctly be called meningopathy, or whether it is due to an increased production of fluid. If the disturbance is due to the latter cause, I do not know any term which could be used, unless it were hydrorrhagia, with a modifying word to indicate its character and origin.

Dr. Frank Fremont-Smith (by invitation): Many years ago Cushing reported cases of a similar condition under the term chronic arachnoiditis, in which I think there was little, if any, evidence for the use of "itis." The clinical syndrome was similar to that in the present cases, and some of the patients were much benefited by suboccipital decompression. Dr. Riley touched on the fascinating problem whether this syndrome is due to increased production or to decreased absorption of fluid or whether there are two groups of cases, the disturbance in some being due to the one cause and in some to the other. So far as I can see

nothing is known as to the etiology and whether it lies in one or the other of these explanations. My idea is that in the majority of cases the condition will prove to be due to failure of absorption rather than to excessive production of fluid. It would be interesting to make a pathologic study of the choroid plexus and the arachnoid villi in such cases. Perhaps Dr. Davidoff has already done this.

One point troubles me: In cases of increased pressure of long duration one nearly always observes atrophy of the brain substance, and this atrophy is almost always demonstrated by internal hydrocephalus. External hydrocephalus due to pressure is almost unknown. The mechanism of external hydrocephalus arising from pressure I cannot understand, whereas internal hydrocephalus follows naturally from pressure, whether the obstruction is in the ventricles or at the arachnoid villi, for the source of the fluid is in the ventricles and there must always be a higher pressure within the ventricles than in the subarachnoid space if there is to be a flow from the ventricles to the subarachnoid space. In the pictures which Dr. Davidoff showed it seemed to me that there was slight internal hydrocephalus, and I wish to ask him whether in these cases the pressure was at the upper limits of the normal. From the theoretical point of view it is hard to understand these changes without some evidence of internal hydrocephalus.

Dr. L. Vosburgh Lyons: I wish to ask Dr. Davidoff if he will say something about the manometric studies made in these cases. Second, how long does he think that it is safe to treat patients without surgical interference? Third, what are his criteria for decompression?

Dr. Ira Cohen: I wish to ask Dr. Davidoff to describe the appearance of the brain as he has seen it exposed at the time of decompression. I ask this advisedly, for one case in particular stands out in my mind. It is that of a middle-aged woman on whom I performed operation five years ago. She gave a history of a relatively acute condition for three or four weeks and of what I thought were localizing signs, including astereognosis, which led me to make an exploration without air studies. At operation there was a collection of fluid in the subarachnoid space, and as I watched the brain seemed to ooze fluid. After a negative exploration and decompression, the patient convalesced satisfactorily, with relatively rapid subsidence of the papilledema. She has remained well to the present. The picture on the operating table is something one does not forget in a long time.

Dr. Lawrence S. Kubie: I wish to ask if any studies on permeability have been made in these cases or studies of the dynamics of the cardiovascular system, particularly with reference to the venous pressure. I ask this because it is at least conceivable that a chronic elevation of the venous pressure could produce the picture described by Dr. Davidoff and Dr. Dyke. Such an elevated venous pressure could block reabsorption of fluid from the venous end of the capillaries throughout the parenchyma of the brain, thus constantly increasing the perivascular transudation of fluid, which becomes added to the subarachnoid lake. It is hard, perhaps, to understand how such a chronic elevation of venous pressure can occur without chronic cardiac decompensation, but the point should be ruled out.

Dr. Leo M. Davidoff: In answer to the question of lumbar punctures in these cases, which Dr. Riley raised: I believe lumbar punctures are indicated, and soon after the diagnosis has been made by ventricular air studies. In reply to Dr. Lyons' question the indications for decompression are such a high degree of papilledema and rapidly failing vision that one cannot wait to reduce the pressure by other means, and therefore decompression is done as a preliminary to other therapy, such as dehydration and repeated lumbar puncture. The decompression then serves as a barometer for further treatment. Thus, if one finds the decompression area soft one omits lumbar puncture. A day or two later one may find that it is bulging and perform lumbar puncture.

With regard to a name for the condition I should like to have suggestions. I do not know what name to give it, for I do not know what produces the disease. I think that the cause is an excess of secretion, but I do not know. Possibly some name containing "hypertensive" might do; certainly, I think that "otitic hypdrocephalus" does not cover the situation.

Concerning Dr. Fremont-Smith's question about so-called chronic arachnoiditis, I believe that that term was applied, perhaps erroneously, in cases in which there was a thickening of the arachnoid membrane around the foramen magnum or the optic chiasm. In either case there usually is some obstruction to the outlet of the cerebrospinal fluid and internal hydrocephalus, so that in some cases the condition is justifiably mistaken for cerebellar tumor and operation is performed by a suboccipital approach. In the single postmortem examination we made, the brain as a whole, the arachnoid villi and the choroid plexus were carefully studied, and no pathologic changes were observed; that has been true in the cases reported in the literature.

As to the size of the ventricles, it has been our impression that, if anything the size of the ventricles tends to be smaller than normal, though we have not wished to declare it for we are not sure.

As for the accumulation of fluid, Dr. Cohen has answered this question as well as his own, for he has described the typical appearance of the brain in these cases. Instead of a dry brain, with widened and flattened convolutions, one sees a wet brain, with the subarachnoid spaces distended with fluid; when the arachnoid membrane is broken there is a stream of fluid which rises 10 cm. or more above the level of the brain. This fluid flows off in large amounts, and the pressure, which is high, is at once diminished.

The pressure of cerebrospinal fluid is often as high as 400 or 500 mm. Usually we are guided as to the indications for decompression by the degree and rapidity of failing vision rather than by the amount of cerebrospinal fluid pressure.

Dr. Kubie's suggestions are stimulating. We have made no tests for permeability. As to changes within the venous pressure I do not know what to say, except that there is no evidence in the patient's general condition, which is good in consideration of the amount of intracranial pressure and papilledema. The apparent well-being might perhaps even be used as a clinical criterion. The patient who died was a man with 7 diopters of papilledema; yet he walked around the wards in apparently perfect health. He complained only of failing eyesight.

DR. RICHARD BRICKNER: If the ventricles are assumed to be less than normal size, or even if they are not enlarged, might this perhaps be related to pressure on the brain from the outside? Might one not gain further evidence on this if one knew the state of the ventricles some time after treatment had been established? Have you any information as to the condition of the ventricles after treatment? Do they enlarge somewhat?

DR. LEO M. DAVIDOFF: We have no case in which we have been able to repeat the air studies after treatment. That has been a sore point with us. We would like to repeat the air studies after treatment not only in these cases but in other conditions which are improved with therapy. It is difficult to persuade a patient to have an encephalogram made after he is feeling better.

CHICAGO NEUROLOGICAL SOCIETY

Regular Meeting, Feb. 20, 1936

S. W. RANSON, M.D., *President, in the Chair*

CHRONIC PROGRESSIVE OPHTHALMOPLEGIA (VON GRAEFE'S DISEASE): REPORT OF A CASE. DR. THEODORE T. STONE.

S. R., a single man aged 31, whose family history was unimportant, was seen in December 1935 and stated that he had been well until 10 years of age, when he had an infection of the left middle ear, associated with purulent discharge, which subsequently resulted in marked defect in hearing. At 15 years of age he noticed that the left upper eyelid became heavy. Gradually the heaviness

increased, and after a year or so the lid began to droop and continued to do so until about three years ago. At that time complete ptosis of the left upper lid was present; it has continued to date. Diplopia had been present for the past three weeks.

Neurologic examination failed to show any objective evidence of organic disease of the central nervous system except for the findings in the eyes.

Right Eye.—The movements of all the muscles of the eyeball were limited (paresis). The muscles least involved were the external rectus and the superior oblique. The pupil was round and 3.5 mm. in diameter and reacted abruptly to light, in accommodation and consensually. The fundus and visual fields for form and color were normal. Stereocampimetric fields were normal and showed no central scotomas.

Left Eye.—There was complete ptosis of the upper lid. The movements of all the muscles of the eyeball were limited in every direction to an arc of 15 degrees. The superior rectus muscle was the least involved. The pupil was round and 3.5 mm. in diameter and reacted promptly to light, in accommodation and consensually. The fundus, visual fields and stereocampimetric fields were normal.

Blood examination showed no abnormalities (erythrocytes, 4,300,000; leukocytes, 7,600, and hemoglobin content, 85 per cent). The Wassermann reaction of the blood was negative. Examination of the spinal fluid gave normal results on three occasions; the pressure was 10 mm. of mercury, and there was no spinal block; globulin was absent, and the colloidal gold (Lange) reaction was negative. The last examination of the spinal fluid was made in December 1935. Roentgenographic study of the skull gave normal results.

Chronic progressive ophthalmoplegia is a rare degenerative disease, which was first described by von Graefe. According to Uhthoff, it occurs in 14 per cent of all cases of chronic ophthalmoplegia. The onset and course usually are: gradual onset of ptosis (usually unilateral) and spread of the paralysis in the course of many months or years to all ocular muscles on both sides in such a way that the internal muscles are spared. In the advanced stages the eyeballs become immobile and do not respond to any voluntary impulse; there is also involvement of the internal muscles of the eye. Development of these signs may take from fifteen to forty years. The process may become stationary. The pathologic condition is said to be hypoplasia or abiotrophy of the third, fourth and sixth cranial nerve nuclei, mainly in the floor of the third ventricle and the aqueduct. Ophthalmoplegia of this type should not be confused with the usual precursory or local symptom of a complicated disease of the central nervous system, such as tabes dorsalis, dementia paralytica, polioencephalitis superior or inferior, multiple sclerosis, atypical form of progressive bulbar paralysis, progressive muscular atrophy, congenital or hereditary ophthalmoplegia, myasthenia gravis or ophthalmoplegic migraine.

DISCUSSION

Dr. D. M. Olkon: Was the pupil on the affected side of the same size as that on the other? Did the patient have double vision?

Dr. Theodore T. Stone: The pupils were of the same size. There was no double vision.

Dr. Eric Oldberg: The following case may be of interest to Dr. Stone. An unmarried farmer aged 29 first noticed that he had diplopia eight months before his admission to the hospital. About a month after the onset of diplopia he noticed that the left pupil was larger than the right. Two months later (five months before his admission), he began to have headaches in the frontal region, particularly referable to the left orbit, which were not associated with vomiting; he also noticed ptosis of the left lid.

Some weeks later he was admitted to the hospital for the first time. There were no findings except practically complete left ophthalmoplegia, the only remaining function being a slight contraction of the pupil to light. All serologic reactions at the time of this admission were negative, and the dynamic features of the spinal fluid were normal. The patient was given antisyphilitic treatment empir-

ically, consisting of bismuth and arsenic, by his local physician in Decatur, Ill., who also repeated the Wassermann and Kahn tests of the blood, with negative results.

As the patient showed no improvement, he was readmitted to the hospital about eight months after the initial diplopia; roentgen examination of the skull showed that the sella was enlarged in a manner typical of a pituitary adenoma. The visual fields were normal.

I performed operation on Jan. 22, 1935, and observed thickening of the chiasmal arachnoid, which I opened, with the escape of considerable fluid. The sella itself was virtually empty, and both optic nerves and the anterior portion of the chiasm were free, as far as I could see.

Since, the patient has had a rather rapid and almost complete recovery of the ophthalmoplegia. The ptosis has disappeared; the left pupil is very slightly enlarged, and there is still slight external deviation of the left eye. The headaches have improved markedly, although they have not entirely disappeared.

DR. PAUL C. BUCY: Did Dr. Oldberg's patient have purely external ophthalmoplegia, as in this case of Dr. Stone's?

DR. ERIC OLDBERG: There was complete palsy of the third nerve in my case.

HYPOPHYSIAL ADENOMA ASSOCIATED WITH PARALYSIS OF THE LEFT SIXTH CRANIAL NERVE WITHOUT INVOLVEMENT OF THE OPTIC CHIASM: RECOVERY WITH ROENTGENOTHERAPY. DR. MEYER SOLOMON.

A white woman aged 32 was admitted to the Mount Sinai Hospital on Nov. 8, 1934, and was discharged on December 4. She was then followed in the outpatient department. The onset and course of the illness were essentially: (1) The menses changed in 1932 from a period of three or four days to one of eight or ten days, with increased bleeding; amenorrhea had been present for nine months. (2) A ring worn on the left index finger had to be enlarged in 1933; hats and shoes which formerly had fitted had become too small since the summer of 1934. The face, especially the cheeks and nose, became enlarged several months before her admission. (3) For a few months she had complained of blurred vision, which had recently been followed by diplopia on looking to the left. In the latter part of October 1934 a left internal squint developed, with inability to rotate the left eyeball outward, and there were occasionally twinges of pain in the left eye. (4) Insomnia had been present since the summer of 1934 and may have been due to domestic and economic problems. (5) There was severe pain in the left eyeball two nights before admission to the hospital. This changed within twelve hours to severe bilateral headache in the frontal region and pain behind the eyes, which was "as though something was pushing the eyeballs out of their sockets." This condition persisted until and after admission to the hospital, with a few attacks of nonprojectile vomiting during the two days preceding admission. The patient entered the hospital because of diplopia and headache.

The patient had been married for seven years and had one child, aged 6 years. She had separated from her husband in August 1934, fifteen months prior to admission to the hospital. The husband later contracted syphilis and received treatment in the outpatient department. The patient said that she had had no sexual relations with her husband (or any one else) during this period, until one month before admission, after a doctor had stated that the husband's condition was noncontagious.

Neurologic examination gave negative results, except for left internal squint, with paralysis of external rotation; the left palpebral fissure was slightly narrower than the right, and the patient was mentally sluggish. She complained bitterly of bilateral frontal headache, deep pain behind the left eye, nocturnal insomnia and drowsiness during the day.

The features, especially the nose and cheeks, were thick. During the first week in the hospital the rectal temperature ranged irregularly from 100 to 101 F., on one occasion reaching 102 F.; for three weeks thereafter it ranged from 99.2

to 99.8 F. Routine examination of the urine and blood, including Wassermann and Kahn tests and estimation of the sugar and urea nitrogen contents gave normal results. The basal metabolic rate on one occasion was + 5 and on another + 13. The sugar tolerance was normal. There was an increase in the intake of fluid (from 2,000 to 4,000 cc.) and in the output (from 3,000 to 5,000 cc.). The blood pressure was 185 systolic and 110 diastolic. A short systolic murmur was heard over the aorta. The ears, nose and throat were normal. Visual acuity and visual fields (form and color), maculas and optic disks were normal. Examination of the spinal fluid revealed normal pressure, sugar, chloride and globulin contents, Wassermann reaction and cell count (5 cells).

Roentgenologic examination on Nov. 8, 1934, revealed enlargement of the base of the great toe bilaterally; otherwise the hands and feet showed no changes typical of acromegaly. The optic foramina were normal; anteroposterior films revealed nothing abnormal; lateral films showed ballooning of the sella turcica, with erosion and rarefaction of the dorsum sellae and posterior clinoid processes, which were visualized as a spur of bone. Shadows of the blood vessels were marked.

The following conditions were discarded in diagnosis: neurosyphilis, including gumma of the hypophysis; encephalitis; multiple sclerosis; intra-orbital lesion; meningioma arising from the sphenoid ridge; aneurysm of the left internal carotid artery; chiasmic arachnoiditis; suprasellar meningioma; glioma of the optic chiasm and nerves; craniopharyngioma, and hypophysial lesions other than adenoma.

Clinical evidences in favor of a hypophysial adenoma were: the sequence of events; the incipient acromegalic syndrome; the age of the patient, and the roentgenographic findings indicating an intrasellar lesion. The palsy of the left sixth cranial nerve was unusual and would commonly occur late if present, but it might be explained by rupture or lateral pressure to the left; in the same way the pain in the left eye might be accounted for. The absence of bitemporal or other hemianopia and atrophy of the optic nerve could be explained by the early prechiasmic stage and by the growth lateral, to the left, rather than upward and forward. The fever for one week on the patient's admission to the hospital was regarded as coincidental rather than of hypothalamic origin, as was the vascular hypertension. The increase in intake and output of fluid might have been of hypothalamic origin; however, it would be less likely to occur, if at all, with pressure laterally. There was no indication for encephalography or ventriculography.

As there were only slight symptoms of an expanding lesion (headache, mental dulness and paralysis of the left sixth cranial nerve) and no involvement of the optic chiasm, roentgenotherapy rather than surgical intervention was employed.

Dr. Gerhard Danelius, of the roentgenographic department of the Mount Sinai Hospital, gave the patient eight high voltage roentgen treatments (November 23, 24, 26, 27, 28 and 30 and December 1 and 3). One field was treated daily, with four portals of entry, one anterior, one superior and two lateral. Irradiation was given twice to each portal, the dose being 1,600 roentgen units on the skin and about 650 roentgen units on the hypophysis. Because of definite improvement in the condition, with no sign of relapse, the treatment was stopped.

All symptoms gradually disappeared, and by March 6, 1935, three months after cessation of roentgenotherapy, the menses had occurred twice (January and February 1935), after an absence of one year. The left sixth cranial nerve palsy and the acromegaly had entirely disappeared. The blood pressure was unchanged. On Feb. 19, 1936, the blood pressure was 200 systolic and 120 diastolic; the intake and output of fluid were not rechecked.

Roentgenograms made on Feb. 10, 1936, showed a markedly changed picture as compared with that before treatment. The sella turcica was still about twice the normal size; both anterior and posterior clinoid processes were evident. The outline of the sella was smooth, except for slight angulation.

The special features to be emphasized are: (1) the early occurrence, without involvement of the optic chiasm or compression of the temporal lobe, of paralysis

of the left sixth cranial nerve and (2) the value of roentgenotherapy in these cases, as compared with that of surgical intervention. Some neurologists would probably have favored operation, and some neurosurgeons would have operated. The case, therefore, brought up for discussion the entire question of roentgenotherapy versus surgical procedure in cases of hypophyseal adenoma, with their indications and limitations.

DISCUSSION

DR. ERIC OLDBERG: The standard treatment for eosinophilic adenoma of the pituitary body is roentgenotherapy. The guide for stopping treatment is the condition of the optic fields. If the fields diminish after treatment starts I believe that one must operate, but if not I continue the roentgenotherapy.

DR. PERCIVAL BAILEY: I have had similar experience with patients with this condition. A woman aged 45 or 46, who had one child, aged 15 years, had not been pregnant since this birth, and the menses had ceased for several years. She also had had the usual symptoms of acromegaly. The fingers were thickened so that she could not wear her wedding ring, and her features had enlarged so that she was ashamed to be seen; she was much distressed by these alterations. There was no change in the visual fields. The diagnosis was made from the condition of the soft tissues of the body and a roentgenogram of the sella turcica, which showed that it was balloon-shaped. Roentgenotherapy was administered and the menses recurred. The patient became pregnant; reluctantly, an abortion was performed. I do not know how to explain the action of the roentgen rays, except that perhaps they cause shrinkage of the growth and lessen pressure on the hypophysis.

DR. MEYER SOLOMON: I wish to ask whether physicians who have observed more of these tumors than I have seen palsy of the sixth cranial nerve, especially in as early a stage as in this case. Not many authors mention this possibility. For example, Bailey, in his book, entitled "Intracranial Tumors" (Springfield, Ill., C. C. Thomas, Publisher, 1933) in discussing the extension of hypophysial tumors lateral to the optic chiasm, does not mention the possibility of oculomotor nerve paralysis, nor does Loyal Davis in his book "Intracranial Tumors Roentgenologically Considered" (New York, Paul B. Hoeber, Inc., 1933). O. Foerster (Ueber die Nachbarschaftssymptome der Hypophysentumoren, *Med. Klin.* **25**:925, 1929), quoted by Grinker in his book "Neurology," mentioned the possibility of involvement of the third, fourth and sixth cranial nerves from lateral extension of a hypophysial tumor, in conjunction with pressure on the tip of the temporal lobe, with associated homonymous hemianopia and so-called uncinate fits; but these phenomena are regarded as late rather than early; nor did Foerster mention the possibility of the occurrence of isolated paralysis of the sixth cranial nerve.

DR. PERCIVAL BAILEY: I do not recall seeing a patient with sixth nerve palsy arising from adenoma of the hypophysis. I should think it unlikely that, if there are no visual findings, the tumor would cause enough pressure to produce palsy.

DR. ERIC OLDBERG: My experience is the same as that of Dr. Bailey. I cannot remember seeing sixth nerve palsy associated with small pituitary tumors. I have seen third nerve palsy in a number of cases of large tumor, as, of course, has Dr. Bailey. The finding in this case is of interest.

THE VIBRATION SENSE. DR. LEWIS J. POLLOCK.

This article will be published in full in a later issue of the ARCHIVES.

THE PSYCHOLOGIC ASPECT OF PSYCHOGENIC SOMATIC DISEASE. DR. KARL A. MENNINGER, Topeka, Kan.

This paper is the extension of a discussion of general and focal suicide and relates in particular to the way in which destruction tendencies may in some instances be carried out on the body itself. I shall begin with a consideration of

the teleologic or functional conception of illness, as opposed to the causal or resultant conception generally prevalent, and pertinent to this I shall make a comparison of the psychologic aspects of hysteria, self-mutilation and organic disease. All these represent the effect of a self-directed attack resulting from various admixtures of the destructive impulses and neutralizing elements; organic disease represents a greater domination of the process by the destructive impulses because of a less degree of erotic neutralization.

The economic principle of sacrifice is presented as a basis for the interpretation of the choice of disease, the purpose of the ego being to make the best possible bargain in the defense of the personality against the powerful destructive impulses which have been reflected back on the self through the threats of reality and the conscience. If they are neutralized completely there are no symptoms; if almost completely, hysterical symptoms occur; if very incompletely, organic disease arises.

At least two problems remain unsolved: first, the question of how and when the conflict relating to organic self-destruction, if such exists, can be brought into consciousness and, second, how these conflicts can be forced into expression through involuntary muscle and the autonomic nervous system. The answer to the first question must be deferred for a presentation of clinical data. The answer to the second will be discussed by Dr. Leo Stone.

PSYCHOGENESIS OF SOMATIC DISEASE: ORGANIC ASPECTS. DR. LEO STONE, Topeka, Kan.

In this paper I propose to establish a consistent theoretical basis for the concept implied in the title, with apology for the speculative nature of part of the text and for the free interpretations of the scientific work of others. The contributions of Cannon and his co-workers are important, especially with reference to the profound physiologic changes which may accompany emotion and to the possible dissociation between voluntary musculoskeletal activity and the inevitable responses of the thalamic-hypothalamic neural level. A correlation between the latter level and the id of psychoanalysis may be attempted, while the cerebral cortex is correlated with the ego. The neural interplay between the cortex and the thalamic level, both centripetal and centrifugal, may be emphasized, and the importance of emotional or instinctual factors in so-called intellectual phenomena may be developed on an organic neurologic basis. Reference is made to the anatomic basis or representation of certain phases of psychosexual development, but the importance of individual psychic experience is recognized. The deep physiologic derivation of speech and thought as clinical material is stressed.

The concept of a dynamic unconscious mind as consistent with the facts of organic biologic structure is developed by reference to a "structuralized phylogenetic unconscious," as revealed in certain neurologic disorders, in which primitive levels of the nervous system dominate the patient's activity. The individual adult unconscious is thought to be physiologically instead of anatomically blocked from stimulating the corticospinal (voluntary) portion of the nervous system. Such endogenous reversible block (repression) is thought to foreshadow the structural inhibition of organic evolution. It is pointed out that psychic aggregates which are blocked from higher levels retain connection with the thalamic-hypothalamic level and that their specific energy is turned with heightened and persistent intensity on the viscera and body fluids.

A fundamental distinction between conversion hysteria and organic disease is attempted. The pathophysiologic features of hysteria are considered preponderantly on a cortical level, psychologically revolving about a problem of object choice rather than a deep disturbance of the instincts themselves. The conversion symptom may be accompanied by mild reversible vasomotor changes, perhaps of cortical origin. The resemblance of certain hysterical symptoms to those caused by small cortical lesions is mentioned. The availability of cortical expression to primitive impulse is thought to vary inversely with the degree and depth of instinctual admixture in a given impulse, because of external risk, while the intimacy of connection with the thalamic-hypothalamic level is thought to vary

directly with the same factors. Thus, the earlier and more profound the psychic disturbance, whether endogenous or experiential, the more liable it is to cause disturbance of any of the numerous biologically important diencephalic functions, with a relative absence of symbolic localization (important in hysteria), and thus the anlagen or materializations of profound organic disease.

An effort is made to equate psychosis and organic disease, since they represent alternative expressions of profound instinctual or vegetative disorder, the cortex being overwhelmed by the diencephalic level in one and the cortex being spared in the other while the viscera are attacked. The severe physical symptoms which may occur in the prodromal period of psychosis to be displaced later by the eruption of mental symptoms, the vegetative disorders of schizophrenia and the frequent relationships between epileptic seizures and psychotic manifestations are mentioned in this connection.

The organic significance of thought and speech as manifestations of complete and partial motor inhibition is considered, and their rôles as modes of instinctual conveyance are discussed. The increasing facility of external adaptation in organic and psychic development is thought to be correlated with increasing danger of organic destruction because of instinctual inhibition. The decreasing death rate from exogenous diseases is contrasted with the static or increasing death rate from endogenous or degenerative diseases. The latter, in my opinion, are especially worthy of deep psychologic study, without deprecation of conventional modes of therapy, despite the fact that such study may not necessarily be successful from either the investigative or the therapeutic point of view.

DISCUSSION

DR. MEYER SOLOMON: It seems to me that these two papers, interesting in their presentation, bring up the old discussion of the influence of so-called mind on so-called body. I say "so-called" because the terms mind and psyche are frequently used in a loose and slippery fashion, as though the "mind" were an entity. In fact, these terms are used in so many vague and different senses that one may not know just what a particular writer means. If the term mind is used for activities accompanied by thoughts, ideas, wishes, feelings, attitudes, etc., the mind is a part of the body. Even insurance companies use the term in this way, as shown by the experience I had some time ago. In the clauses of the company referring to permanent total disability mention was made only of bodily or physical disease or accident. In reply to a query whether this included mental diseases and disorders the insurance company stated that as the mind is a part of the body mental diseases and disorders were intended to be included in their written clause. One should therefore, I believe, speak of mental and nonmental bodily activities. The problem, then, is: How and to what degree are so-called mental (really mental bodily) activities accompanied by nonmental bodily activities? The latter may be divided into postural, skeletal, proficient, ambulatory or voluntary and vegetative, visceral, autonomic or involuntary activities. These papers brought up the possibilities of the direct and indirect influences of thoughts, ideas, wishes and willing on the skeletal and vegetative systems. I think that there is much evidence to show that ideas, whether in normal conditions or in states of increased suggestibility associated with hysteria or hypnosis, if unaccompanied by emotion, can produce changes in the skeletal system directly and immediately but that the vegetative system can be affected by ideas only indirectly, secondary to and supportive of primary changes in the postural system. If that is so, I cannot see how by supposedly unconscious mental processes, whether in the form of ideas or wishes, direct manipulation of the involuntary system can occur. Even in so-called voluntary control of the heart beat, I believe that careful study will show that the subject adopts certain postural attitudes, the whole organism being thrown into a certain mental attitude (excitement, anger, fear, anxiety, etc.), skeletal tension and visceral upheaval, part of which is a rapid heart beat. There is thus really present a tense state, which is more properly emotional behavior.

In emotional reactions there is a different situation than in suggestional behavior. If emotion is defined as excited activity of the total animal machine, with the

organism acting as a whole, with conscious activities and skeletal and visceral reactions, I cannot see how there can be such a thing as unconscious emotion. Of course, this whole question brings up the controversy whether there is a so-called unconscious mind. In the work of Pavlov on conditioned reflexes one finds much the same thing. The conditioned reflexes or responses are part of the reaction of the organism as a whole, with attitudes of anxiety, apprehension, etc. Excitement has been defined by Stratton as undifferentiated emotion.

As to hysteria, I happen to be one of those who cannot conscientiously use the term conversion hysteria because of the connotation and conceptions back of the term conversion (especially the assumption of the existence of an unconscious mind capable of thinking, wishing, willing and acting). I prefer the use of the old-fashioned term hysteria, simple and unqualified. In the two papers presented this evening the idea was expressed that the symptoms in hysteria are active, symbolic psychologic symbols, produced by the so-called unconscious mind, which was actively working at the moment to produce and continue the symptoms. The symptoms are thus regarded as actual thought presentations in the body at that particular moment. What actual concrete evidence is there to support this contention?

In general, I think that these two papers bring up the question of the whole relationship of the skeletal and vegetative systems, of how ideas can influence, directly or indirectly, the vegetative system and whether ideas can affect the vegetative system without primarily influencing the skeletal system. I should like to know particularly how emotion can be an unconscious process, going on and persisting in an unconscious mind, when emotion is really, clinically, a total upheaval of the organism from its highest to its lowest levels.

DR. FRANZ ALEXANDER: I shall restrict myself mainly to a few historical statements. Dr. Menninger was fair in stating that he assumes full responsibility for extending the theory of conversion hysteria to organic disturbances. I think he went too far in assuming responsibility for this. Freud, himself, never did, but some of his followers played with the idea that organic disturbances may also, in certain cases, be explained on the same basis as conversion hysteria. Of these Dr. Felix Deutsch recently reconsidered this theory and made important qualifications.

The fact that emotions have an influence on vegetative functions is, of course, well established. The question is whether specific ideation, which can, for example, produce paralysis of an arm, can in the same specific way also influence all vegetative organs. There is no real evidence in the literature for such a possibility. There are considerations which make it highly improbable that such a specific influence is possible. Most of the vegetative organs are known only from books on anatomy. There is no direct knowledge of them. It is hard to imagine that one can use the stomach to express an idea in the same way as one can use the larynx or the hands, with which one can make expressive movements, or the facial muscles, by which one can express even specific emotional conflicts. If one does not study anatomy one will not know that one has a stomach, and I cannot imagine that the stomach can express such a specific idea as that of suicide. I can imagine that an emotion can increase the secretion of the stomach in the way Pavlov has shown. Such functional disturbances of the stomach in time and under certain conditions may lead to an organic change. I think it is premature and radical to assume that an ulcer in the wall of the stomach, caused probably by hyperacidity and certain changes in motility, is intentionally developed as an expression of self-destructive tendencies. I cannot imagine that the vagus nerve has specific self-destructive fibers. The functions of the stomach are limited. It can contract and secrete. Similarly, the functions of all internal organs are limited to such vegetative accomplishments. The function of the larynx, however, is suitable to express thoughts through very finely differentiated motor processes: by speech. The stomach by its very structure has no such possibilities. It has no specific function which would make the stomach suitable to express a specific idea. I do not agree with Dr. Menninger and Dr. Stone if they intend to show this, but I think they both demonstrated beautifully that emotional factors can

influence organic functions and lead even to organic changes. I cannot accept, however, that a self-destructive instinct—one does not know for sure whether there even is such a thing—expresses itself directly in an organic structural change, in a destruction of tissue. It is known that functional disturbances have often an emotional basis. The emotional influence, however, does not necessarily always consist of a self-destructive wish. Any emotion which is definitely associated with an organic function can influence this function. If a dog is conditioned to an acoustic stimulus this stimulus will precipitate the secretion of gastric juice. From psychoanalytic studies on patients suffering from duodenal ulcer, it seems that, like acoustic stimuli, certain repressed wishes can also lead to hypersecretion and ultimately to formation of an ulcer. These wishes, however, are not necessarily of a self-destructive nature. Such a concept seems to me in much better accord with known physiologic behavior. I do not think that one will be able to demonstrate in the vegetative nervous system certain fibers which can conduct specific ideational content, and unless one can the attempt to explain the psychogenetic influences on vegetative organs in the same way as one explains hysterical symptoms will remain a theory. My attitude is that this theory is unnecessary, for it is possible to explain these influences without making the assumption that the vegetative nervous system can express intentions in the same way as the voluntary. I am a little skeptical about the use of deductive methods in such a complex field as this, and I prefer the use of induction.

Dr. Lewis J. Pollock: I was delighted to hear Dr. Stone's closing statement that it is necessary to put these ideas to the test of research. That is true; certainly, no one will take exception to it, however crystallized an organicist he may be. I have a simple type of mind and find it difficult to place on paper any conception of what I expect to find by a projected type of research. One should find out what will occur under certain conditions, and then one can discuss them. One cannot state that an endogenous stimulus resulting from an unconscious trend will bring about certain things. I do not know at all what will happen, but it is permissible to say that one will see. If the idea is put to some actual proof there will be little antagonism from any one. That emotion in a wide sense has a relation to some physical state is not a new idea. In reading a textbook recently I investigated the causes of various diseases; among them I found that paralysis agitans is caused by fright and fear and that combined degeneration of the cord, epilepsy, multiple sclerosis, amyotrophic lateral sclerosis and many other conditions were said to be caused by fright and emotional disturbances, exposure to cold, fatigue and so on. It struck me at the time how wonderful it would be if one could get rid of fright, cold, exposure and so on, but then there would be no need for neurologists.

I have no doubt that in dealing with some organic diseases it has been possible to elicit functional conflict, but to state that this is the cause of the disease is going too far. If one were to have this unconscious wish or urge for self-mutilation or destruction, it must await some happy circumstance before this can occur. A man must have the opportunity to live in Brazil before he can acquire infection with a trypanosome and suffer from Chagas disease. It was necessary to transport the spirochete to America before one could acquire syphilis, or one must be fat and overeat before one can suffer from diabetes. The man must have not only the wish for self-destruction but the opportunity for the development of a particular disorder. Otherwise, one must conclude that this wish produces boils, that wish produces diabetes or another wish does something else. One of these two circumstances must be true.

In general the fact that one determines that an exciting factor exists in disease in no way proves that it causes the disease. All forms of excitants are present in all types of disease, and while it is not difficult to say that by emotions there may develop a change in the body of a chemical or other nature which, combined with a particular infection, leads to a boil, this may be only nature's way of giving the woman something to think about—like a dog's fleas. I believe that if one is to consider barometric changes as responsible for various things they should

be put to the test, and likewise changes in the function of the autonomic nervous system. The thing is to produce such changes in an animal and see what happens. Then one may be able to entertain this relationship in regard to organic disease. Until that is done all one can say is that one recognizes the relationship of emotional changes to various bodily states, for these are what nature intended to the end that the animal may adjust to its environment. One must go into the laboratory and demonstrate.

DR. ROY R. GRINKER: The presentation of Dr. Leo Stone has interested me greatly. It does not offend my strictly organic background as it seems to that of Dr. Pollock, but as a neurologist I find that the psychiatric thinking which Dr. Menninger and Dr. Stone have placed before the society is the only kind acceptable because of the very nature of present day neurologic concepts. Since the days of Hughlings Jackson, it has been customary to think in terms of forces released from inhibition, changes in direction and quantities of neural energy. Inhibition and repression cannot be thought of as two different concepts but as representing the same fundamental idea. In neurologic diseases, it is true, the lesions which cause a release of inhibition are gross and demonstrable. In the field of psychiatric disturbances it may be that the lesions are not demonstrable merely because of the lack of appropriate technics, such as chemical methods. It is more likely that the fundamental basis is in itself a change in the direction of forces working at a higher level and, hence, simply exemplifying the adaptability of the human neopallium.

Nevertheless, I am not prepared to talk of psychologic factors in neurologic terminology. It is true that when a new science is incorporated into the general body of science the new hypotheses are restated in terms of better proved theories. Such a translation in terminologies and mechanisms from one field to the other is an interesting speculative process, but it is fraught with the danger of inaccuracies and may form a resistance to further psychologic work. It is this particular field of correlation between the structures concerned in the disturbances of function in the field of mental disease that requires man as the experimental animal. Laboratory and animal research must play a secondary rôle in these psychiatric problems which appear only in the human animal.

I wish to congratulate Dr. Menninger and Dr. Stone on their attempts at the correlation of neurologic and psychiatric concepts, even though it is my belief that it is premature and inaccurate. It serves to call attention again to the fact that the activity of the nervous sysem, whether in terms of gross organic disease or in the field of neuroses, must be considered as obeying the same general fundamental laws of biologic behavior.

DR. KARL A. MENNINGER: Dr. Stone will answer the comments of Dr. Pollock and Dr. Grinker, and I shall address myself to Dr. Alexander's objections.

Schopenhauer once wrote an essay on the technic of dealing with an adversary in public debate. One method he advocated was that of misquoting the opponent, changing what he said to something obviously ridiculous and then holding this up as representative of his logic and point of view. This, it seems to me, is what Dr. Alexander has done with us. In his critical comments on our paper he disclaims belief in the existence of ideas of destruction, of ulcer formation, traveling down the vagus nerve to the stomach. Such a preposterous concept certainly never entered my head, nor does it appear anywhere in my paper. The words were Dr. Alexander's and not ours. I spoke of self-destructive trends, not self-destructive nerve impulses. I said that self-destructive trends might appear ideationally, behavioristically and organically; I expressly disclaimed any belief in the primacy of the ideational content. I think, and this is what I said and I believe it is also what Dr. Alexander believes, that, fortunately, one may sometimes obtain a notion of the motive lying behind certain skeletal and organic behavior by consideration of the ideation which accompanies this behavior and which presumably originates from the same instinctual sources. Sometimes it is more practical to read the language of behavior than the language that comes from the larynx, for, as Dr. Alexander himself has pointed out, speech is often only a device for con-

cealing rather than for expressing thoughts. That actions sometimes speak louder than words is well known; I have suggested that the behavior of organs may sometimes speak louder still.

Obviously, I do not refer everything to self-destruction. If an earthquake should occur this minute and destroy the building in which this society is meeting I should not regard that as due to self-destructive trends in any one. If, on the other hand, an individual person in this audience should get up and shoot himself I should think that that was self-evidently self-destruction. I think it is possible to show that the impulse which causes a man to shoot himself may find forms of expression other than this.

Aside from this polemic difference with Dr. Alexander, I think we are much in agreement. The magnificent work done at the Institute for Psychoanalysis, particularly in regard to the psychogenic factors in gastro-intestinal disease, seems to me to substantiate the theory that Dr. Stone and I have elaborated this evening. It is not clear to me in just what way Dr. Alexander really differs with us.

Perhaps it is chiefly a philosophic or methodologic difference. Dr. Alexander (and in this Dr. Pollock concurs with him) is in a mood for extolling the empirical, inductive method and rejecting the deductive method of scientific approach. No one can quarrel with the accepted fact that to collect and measure observations, arrange them according to some system and attempt to interpret them according to some law is a valid scientific approach, but to assume and maintain that this is the only method of scientific approach is, I think, an obvious fallacy. There are other scientific approaches and methods, for example, the one which Prof. J. F. Brown (Kansas) calls the hypothetic-deductive method or the one which Prof. Mortimer Adler (Chicago) calls the philosophic (as contrasted with the statistical) method. The point is that to advance a hypothesis ahead of the facts is sometimes not only permissible but actually essential if one is to arrive at certain more elusive truths. Columbus would never have discovered America if he had depended on the empirical or inductive method to which Dr. Alexander is at the moment so whole-heartedly committed. The whole trend of thinking in modern physics, for another example, depends much more on the hypothetic-deductive than on inductive methods. I see no reason why one cannot apply the same methods of approach to problems of psychology. In this I have the good example of Aristotle and Freud, not to mention more recent explorers.

Dr. Leo T. Stone: I am not capable of settling any philosophic questions. I cannot argue with Dr. Pollock, for I agree with him entirely in many things he has said. In fact, I think I said the same things in my paper. However, I do not agree with him that all these matters should be settled in the laboratory. I agree rather with Dr. Grinker that the crucial settlement of these problems must be made with man himself as the "laboratory animal." There is perhaps an important difference between Dr. Pollock's opinions and our own, but that is mostly, I believe, in the sphere of unexpressed attitudes. Having had a rather rigid neurologic training in good hands a few years ago, even though I may not have profited by it, I think that I, too, have been bound by some of the same bias expressed or implied tonight, and it is probably for this reason that I undertook the writing of this paper. Because I felt intuitively that there was much truth in some of Dr. Menninger's ideas and had observed many perplexing clinical phenomena along these lines, I wished to provide a rationale for the investigation of these phenomena and for understanding them from the organic point of view. Such methods do not settle important problems in medicine or in other fields, but we believe that the giving of intelligent direction to work is perhaps a small, but not entirely unimportant, contribution.

We do not think that our papers have settled anything conclusively, and we did not pretend that they did. On the other hand, I am not sure that all physicians, especially those with rigid organic background, would agree on the advisability of conducting deep psychoanalysis in persons suffering from disease of the coronary arteries or general degenerative arterial disease, unless they could see reasonable possibilities in such an effort at the beginning.

Dr. Solomon mentioned some matters which I believe referred to my paper. I thought that I made clear in the paper what I meant by the word emotion.

I do not believe that this meaning differs radically from that mentioned by Dr. Solomon. I did emphasize, however, the fact that the complex organism is often inhibited from reacting in total, that is, in instinctual, patterns and that for this reason some manifestations of emotion are heightened and distorted. We tried also, I believe, to answer another of Dr. Solomon's questions in the text of the paper, that is, the question regarding reasons for belief in the presence of an unconscious mind. If one turns to the psychoanalytic chamber, or even to less cloistered methods of psychotherapy, one can see hitherto unconscious emotions in actual eruption. This does not, of course, demonstrate conclusively that they are present coincident with ordinary life activity. In clinical neurologic practice, too, one can see evidences of the existence of unconscious emotion. If a patient suffers bilateral hemiplegia, that is, pseudobulbar palsy, one may observe the emergence of involuntary laughter and crying, whose origin the patient himself does not understand. Such observations, of course, are not proof of the presence of the unconscious, but they are interesting bits of evidence toward establishing the existence of a phenomenon which so satisfactorily explains much that would otherwise have to remain entirely unexplained.

I have no point of difference with Dr. Grinker. From purely organic considerations I cannot argue with Dr. Alexander. I believe that Dr. Menninger has already discussed Dr. Alexander's point of view on a psychologic and psychoanalytic basis and that he can argue this matter further if there is sufficient time.

PHILADELPHIA NEUROLOGICAL SOCIETY

Regular Meeting, Feb. 28, 1936

FREDERIC H. LEAVITT, M.D., *President, in the Chair*

ACUTE LYMPHOCYTIC MENINGITIS. DR. JAMES W. WATTS, Washington, D. C.

Two patients with severe headache, vomiting and clinical signs of meningitis were observed at the Massachusetts General Hospital in August 1928 by Dr. H. R. Viets and me. When 143 and 233 lymphocytes, respectively, were observed in the cerebrospinal fluids, the patients were thought to have tuberculous meningitis. The protein in the spinal fluid was increased in the early stages of the disease. The sugar and chloride contents were within normal limits. There was no pellicle. No organisms were observed in smears or cultures. Inoculations of guinea-pigs for tuberculosis gave negative results. The Wassermann reactions of the blood and spinal fluid were negative. The disease in each instance ran a subacute course, and the patients recovered.

These cases could not be classified as instances of meningitis of any known type and were described in a preliminary report under the name of aseptic (lymphocytic) meningitis (Viets, H. R., and Watts, J. W.: *New England J. Med.* **200**:633, 1929).

During February and March 1929 we observed 3 more patients with aseptic (lymphocytic) meningitis. Like the other 2 patients, these presented a clinical picture of tuberculous meningitis. Repeated examinations of the cerebrospinal fluid revealed an exclusively lymphocytic formula, elevation of the amount of protein and normal contents of sugar and chlorides. The relatives of the patients were told that the disease was an unusual type of meningitis which runs a course of from three to six weeks and that recovery is usual. The 3 patients recovered without sequelae.

The symptoms, course of the disease and findings in the spinal fluid were so characteristic that a more complete description of the disease was reported (Viets, H. R., and Watts, J. W.: Aseptic [Lymphocytic] Meningitis, *J. A. M. A.* **93**:1553 [Nov. 16] 1929). It was found that a few cases of a similar condition had been described by Wallgren of the Children's Hospital at Gothenburg, Sweden,

who called it meningitis "aseptica" acuta. Wallgren expressed the belief that the disease was possibly a new type of infection but that it might be related to epidemic poliomyelitis or encephalitis.

In 1934 Dr. Viets and I reexamined our earlier patients and reported cases which had come under observation in the past five years (*J. Nerv. & Ment. Dis.* **80**:253, 1934). During this five year period aseptic (lymphocytic) meningitis had found a place in medical literature. There were 41 articles, describing over 200 cases. Reports came from the United States and from a majority of the European countries.

We found no sequelae in our 15 patients, 5 of whom had been followed for a period of five years. Observations in a larger number of patients demonstrated that when the disease takes a more severe form the pleocytosis is not exclusively lymphocytic but polymorphonuclear leukocytes and a pellicle may be present. However, lymphocytes predominate, and the sugar and chloride contents of the spinal fluid remain normal.

In summary, it may be said that acute (lymphocytic) meningitis, which was first described by Wallgren in 1925, is now recognized clinically as a distinct disease and has been shown by Armstrong and Dickens to be caused by a specific virus (Armstrong, C., and Dickens, P. F.: *Pub. Health Rep.* **50**:831 [June] 1935). Since the disease is caused by a virus, the term aseptic should no longer be applied. It is characterized by acute but relatively mild onset, with headache, vomiting and moderate fever. Recovery is the rule. The cerebrospinal fluid shows pleocytosis which is predominantly lymphocytic, although in more severe forms polymorphonuclear leukocytes may be present. The total protein is usually greater than the average amount found in normal fluid, but the sugar and chloride contents remain within the usual limits.

ACUTE LYMPHOCYTIC MENINGITIS. DR. I. S. HNELESKI.

In the early part of July 1935 there began to appear in the receiving ward of the Philadelphia General Hospital a group of patients who for some time presented a diagnostic problem. Owing to the season of the year and the symptomatology present, the condition in this series was variously diagnosed on admission: typhoid fever, anterior poliomyelitis, meningococcic meningitis, influenza and fever of unknown origin. After admission and observation of the patient, however, the more prevalent diseases were eliminated, and it was concluded that the existing condition was uncommon and clinically resembled the disease reported in the literature by various authors, both in the United States and abroad, as sterile meningitis, acute aseptic meningitis, acute lymphocytic meningitis or benign lymphocytic choriomeningitis.

In this series of 23 patients who were admitted to the hospital between the first of July and the latter part of August 1935 there were 16 males and 7 females, comprising 14 white persons and 9 Negroes. The range in age was from 10 to 50 years, but the majority were in the second or third decade of life. The duration of illness before admission ranged from one to nine days, and the duration of hospitalization varied from three to twenty-three days, averaging approximately ten and one-half days.

The outstanding symptoms were headache, nausea and vomiting, of sudden onset. This triad was outstanding—headache was the most prominent feature of the three and in 1 or 2 cases it was the only symptom; its character varied from mild to very severe. In addition, there were varying degrees of photophobia in 6 instances. Five patients had chills. Two complained of stiffness of the neck and back and 2 of vertigo.

Physical examination revealed evidence of toxicity of varying severity ranging from a mild degree to marked toxic delirium. Four patients showed evidence of generalized abdominal tenderness. Two patients had attacks of epistaxis.

On neurologic examination definite evidence of nuchal rigidity was shown in 10 cases. In 5 instances there was a bilateral Kernig sign; in 15 the evidence was negative as far as Kernig's sign was concerned, while in the remaining 3

this sign was not noted. In most instances the reflexes were considered to be actively normal, and in only 1 case was there a question of the absence of patellar reflexes.

The temperature in a few instances rose to as high as 104 F.; the average duration of elevation was two and a half days, with a range of from one to eleven days. The pulse rate at its highest was 130, but the average was from 90 to 110, while the respiratory rate remained practically normal.

Laboratory Studies.—The outstanding laboratory studies related to the spinal fluid. When examined the pressure invariably showed elevation above normal limits, reaching as high as 20 mm. of mercury. The cell count varied from 30 to 2,100, though in most instances there were below 600 cells. Differential studies showed no definite pattern, but as a rule during the early stage of the disease the polymorphonuclears predominated, whereas in the later stage the picture was reversed and lymphocytes predominated or were present exclusively. Sugar and chlorides were within normal limits. After a spinal puncture patients invariably offered the information that they felt improved.

The white blood cell count varied from 3,600 to 15,600, with no characteristic differential count; in some instances the lymphocytes predominated, but as a rule the polymorphonuclears averaged about 75 per cent.

The Kahn test in all cases gave a negative reaction. The laboratory studies revealed no pertinent information.

The characteristic clinical course in these cases was: In most instances the patient, though acutely ill and very toxic for the time, suddenly improved, and all symptoms disappeared at one time. Recovery was rapid, and no immediate complications were observed.

Unfortunately, no experimental data are available, for just as preparations were being made for experimentation the outbreak subsided.

EPIDEMIC LYMPHOCYTIC MENINGO-ENCEPHALITIS. DR. ERNEST L. NOONE.

This paper is a brief report of a series of 37 cases of epidemic lymphocytic meningo-encephalitis in Philadelphia during the summer of 1935. The children were admitted to the service of Dr. William Bradley at the Children's Hospital of the Philadelphia General Hospital between July 27 and September 15. They comprised one third of all patients admitted to the ward during this time. None of the children, or of the adults, displayed any paralysis, nor was any patient with a fresh stage of paralysis admitted during this period. The disease was communicable, and there was considerable familial incidence. Seven of 36 patients in the series came from 3 families, and 9 other families reported cases of a similar disease either in the same household or among close playmates. The dates of admission were fairly evenly spaced. The majority of admissions were in the month of August. The ages at the time of admission were uniformly distributed between that of the youngest patient at 1 month and that of the oldest at 11 years.

In practically every case the disease was featured by fever, headache and vomiting, and of this triad headache was the most striking. The duration of the disease was usually from three to six days; 3 patients apparently recovered in two days, and the illness in 1 case persisted for nine days. Many of the children appeared profoundly ill; others laughed and joked while they were examined. Eleven children were described as drowsy, somnolent or even stuporous and 6 as hyperirritable. The onset was sometimes abrupt or sometimes insidious, with preliminary headache. Recovery was rapid and uneventful in 36 cases. In 1 case included in this series the outcome was fatal. The condition was believed to be a fulminating manifestation of the same disease.

In every case there was elevation of temperature, the lowest being 99 F. and the highest 105 F. In the majority of instances it reached 101 or 102 F., although in one third of the cases a height of 103 F. or over was attained. In 22 cases in which there were fairly accurate data on onset, the total duration of fever varied from two to seven days.

Headache was the most striking feature. Thirty-five children were of sufficient age for observation, and of these 32 had headache. It was usually severe, tended to be persistent and was most frequently localized in the frontal region, although occasionally it was confined to the top of the head. It usually preceded the vomiting, and in some cases, the fever. Withdrawal of spinal fluid almost always afforded prompt relief. Thirty-one children vomited. In one third (11) the vomiting persisted two or more days. It did not appear to be secondary to gastro-enteritis. In 7 cases some degree of photophobia was manifested. Examination of the eyegrounds was made in 12 instances, and the findings were normal except in 3 cases, in which there was slight blurring of the disks. Four children had chills. Twenty-seven children either had nuchal rigidity or complained of pain on bending the spine. Of these 15 had nuchal rigidity and 18 a positive spine sign. Alteration of the reflexes was not uniform or striking. In 15 children the deep reflexes were hypotonic and in 2 hypertonic; in 17 children they were described as normal, and in 3 instances description was omitted. The tendency was toward a decrease in response.

Examination of the spinal fluid was made in all 36 cases, and more than one examination was made in 27 instances. The total cell counts varied so widely that it was impractical to average them, especially since they differed with the day of the disease. The majority were in the neighborhood of 100 cells. Only three revealed less than 40 cells. The highest count was 650 cells. The cells were chiefly lymphocytes. The tendency was for the number of neutrophils to be higher in the earlier than in the later counts. Increase in cells tended to postdate apparent clinical recovery. In the majority of instances the total number of white cells of the blood was normal or reduced, and it is probable that a lower total count was more likely to occur in the early days of the disease, although in some instances low counts were obtained as late as six or seven days after the onset.

No information of value was obtained from other laboratory examinations.

Material obtained from patients in the acute stage and convalescent serums were subjected to study by Dr. Charles F. Church of the Children's Hospital, Philadelphia; Dr. T. F. McNair Scott of the Rockefeller Institute for Medical Research and Dr. Charles Armstrong of the National Institute of Health, Washington, D. C. The material used was not infectious for guinea-pigs, mice, rabbits or monkeys. Further, the convalescent serums afforded no protection against the virus of acute choriomeningitis. Neutralization tests were negative against the virus of the St. Louis type of acute encephalitis (known as encephalitis B) the virus of poliomyelitis of the Philadelphia epidemic in 1931 and the mixed virus of poliomyelitis.

PATHOLOGIC CHANGES IN A CASE OF FATAL LYMPHOCYTIC MENINGO-ENCEPHALITIS. DR. HELEN E. RIGGS.

The brain and cord in the single case of fatal termination occurring in the epidemic of "headache disease" in Philadelphia showed intense edema and congestion, with gross evidence of diapedesis of red cells into the subarachnoid space.

Microscopic examination revealed degenerative changes in the endothelial cells of the capillary bed and evidence of stasis throughout, with resulting perivascular and pericellular edema.

In the cortex the ganglion cells showed extreme swelling of the cytoplasm, often with rupture of the cell membrane and detachment of the processes. With this change ischemic degeneration was also noted. There was little or no glial reaction except in the nature of mild satellitosis. Similar changes were observed throughout the brain, but cellular degeneration was most severe in the vegetative nuclei of the tuber cinereum and medulla, the Purkinje cells of the cerebellum and the second and third layers of the cortex. Perivascular hemorrhages were present in the periventricular gray matter of the third ventricle. Mild and sparse perivascular infiltration of lymphocytes and mast cells was noted, limited entirely to the white matter. The most intense perivascular cuffing was in the cornu ammonis.

The spinal cord showed thickening and hyalinization of the dura, with proliferation of the arachnoid around the nerve roots. The cord itself was edematous and showed peripheral demyelinization and ischemic degeneration in the anterior horn cells. The vascular changes were similar to those in the spinal cord. There was no evidence of perivascular infiltration or of any glial reaction. A diagnosis of acute encephalitis was made, although the degenerative changes in the ganglion cells and vascular apparatus suggested that the term "toxic degenerative state," as used in the German literature, might be sounder. I hesitated to include this instance in the series of cases of epidemic "headache disease" until I had seen the slides in the case of fatal outcome in the epidemic at Windber, Pa. The cerebral changes in this case were strikingly similar to those already detailed. Communication with Dr. H. A. Slesinger of the Windber Hospital revealed that his patient had been ill less than twenty-four hours and that two other members of the same family had been ill at the same time but had recovered.

From this information it is believed that the present case was an instance of the fulminating form of "headache disease." This supposition was strengthened by the finding of sequelae pointing to organic disturbances in the central nervous system in 12 children, less than six months after the acute disease.

ACUTE LYMPHOCYTIC CHORIOMENINGITIS: EXPERIMENTAL CONSIDERATIONS. DR. CHARLES ARMSTRONG, Surgeon, United States Public Health Service, National Institute of Health, Washington, D. C.

In November 1933 a previously undescribed virus was isolated at the National Institute of Health which has been shown to be pathogenic for rhesus and cebus monkeys, white and wild mice, guinea-pigs and chickens. In experimentally inoculated monkeys the virus became generalized and was demonstrated in every organ or tissue investigated, namely, the adrenals, lymph glands, blood, cerebrum, kidneys, liver, lungs, bone marrow, voluntary and heart muscle, pancreas, salivary glands, spleen, spinal cord and testes.

The usual pathologic changes in the central nervous system of infected monkeys are characterized by swelling, edema and lymphocytic infiltration of some or all of the choroid plexuses, accompanied by irregular to diffuse infiltration of the meninges with lymphocytes.

Acute lymphocytic choriomeningitis is therefore suggested as the name for this experimental disease. The ailment in monkeys is accompanied by a spinal fluid cell count ranging from 150 to 3,000 cells, almost entirely lymphocytes, while the sugar, sodium chloride and urea nitrogen contents fall within normal limits—characteristics which suggest acute aseptic meningitis in man.

The serums of recovered monkeys when mixed with virus in proper dilutions rendered the latter noninfectious for mice. The serums of monkeys recovered from other diseases, including poliomyelitis and encephalitis (St. Louis type), failed to neutralize the virus.

Serums collected from persons with a history of aseptic meningitis have been found to neutralize the virus even after several years. In 3 instances serums devoid of demonstrable antibodies during the attack became strongly protective during convalescence. Numerous instances have, however, been found in which serums from patients whose disease was diagnosed as aseptic meningitis failed to develop antibodies against the virus of lymphocytic choriomeningitis, indicating that this clinical picture may include more than one etiologic entity.

Cases have also been found in which highly potent antibodies against the choriomeningitis virus were shown but the appearance of symptoms suggesting an infection of the central nervous system was denied, suggesting that infection with this virus does not always lead to meningeal involvement. Of over 550 human serums so far tested 6.2 per cent possessed highly potent antibodies against the virus.

From the limited data at hand, it appears that males and females, both white persons and Negroes, are attacked by the virus of acute lymphocytic choriomeningitis and that cases occur throughout the year.

The method of spread of the disease in man is unknown.

DISCUSSION

DR. C. A. PATTEN: I have not had the opportunity of reviewing the papers presented at this meeting, and therefore what I have to say will be in the nature of general impressions gathered while listening to the speakers. First, I am not conversant with the bacteriologic or epidemiologic phases of acute lymphocytic meningitis and can add nothing to their discussion. From the clinical and neurologic standpoints the subject is interesting, particularly with regard to diagnosis and treatment. There are many variations in the manifestations of these disorders, but, withal, there is a great deal in common. The interesting feature of Dr. Armstrong's presentation was that the virus could be obtained from various tissues and organs of the body, indicating a systemic rather than a localized cerebrospinal infection. Attention is diverted by the meningeal reaction because it is so striking, and one overlooks the other phases of the disease.

From Dr. Riggs' lantern-slides it seems that the term meningitis is not entirely adapted to the situation. She has shown that the disease is more than meningitis; it is a meningo-encephalitis. However, little autopsy material has been available to date, and further study is needed. Dr. Leavitt mentioned cases during the past year in which aberrant forms of encephalitis were recognized. All the patients had ocular paralysis but none meningitis, or at least they were not studied early enough to determine this point. These patients usually had sudden onset of symptoms, and the disease ran a typical course, with mild fever and headache. They either recovered promptly or had persistence of neurologic signs for a considerable length of time; some still receive treatment. A complete evaluation of lymphocytic meningitis is a bacteriologic as well as a clinical problem. It recalls the pandemic of influenza in 1918 and 1919, following which a great group of cases was observed of what has since been regarded as chronic encephalitis. At the time of the epidemic everything was "flu," but since that time, with the appearance of certain rather characteristic signs and symptoms, typical encephalitic types have been separated. There is still a question in my mind whether epidemic influenza and encephalitis do not have some etiologic relationship. From the clinical standpoint, however, it is likely that there are several variations of a virus disease, and further bacteriologic and pathologic investigations are necessary.

DR. EDWARD D. ATLEE: When Dr. Leavitt asked me to discuss these papers I was under the impression that there had been in the Temple University Hospital more cases than I could find. During the past epidemic only 5 patients were admitted to the children's ward during August and September whose condition came under that category. Dr. Tyson's diagnosis in these cases was poliomyelitis; in 4 cases, no paralysis developed, and the disease was considered abortive poliomyelitis; in the fifth case temporary paralysis developed on the fourth day. In my private practice I saw 8 or 10 cases of the so-called abortive poliomyelitis. I made no lumbar punctures. All patients had headache, vomiting and stiffness of the neck, which lasted from two to four days, without weakness of any sort. A boy aged 5 years, who had visited at a camp in Delaware in the last week in July, vomited and experienced severe headache a week after returning home; the next morning I performed a lumbar puncture. This revealed a cell count of 290, with 85 per cent polymorphonuclears; the blood count was normal. One hundred cubic centimeters of pooled convalescent serum was administered, on the supposition that the case was one of acute poliomyelitis. No paralysis developed, and I thought I had accomplished something remarkable. I am still under the impression that this boy had true poliomyelitis. Dr. Lucchesi, of the Municipal Hospital, told me that he saw a number of patients there.

DR. ROSS H. THOMPSON: Twelve of the children seen during the epidemic in the summer of 1935 were studied for evidence of organic neurologic sequelae. This preliminary study was made during February 1936, approximately six months after the acute period. Evidence of organic changes in the brain were present

in all cases, but since this is the preliminary report of a more elaborate survey, only a brief summary of the findings will be given.

Symptom	No. of Cases
Impaired convergence	9
Impaired activity of tendon reflexes	9
Choreiform movements	4
Choreiform restlessness	3
Impaired automatic movements of the upper extremity	3
Change in personality	1
Hyperhidrosis	1
Enuresis	1
Somnambulism	1

None of these findings had been noted prior to the acute illness.

DR. P. F. LUCCHESI: Last July my attention was called to the fact that there was an unusual number of cases of acute lymphocytic meningitis. Previously, possibly one-half dozen cases had been reported in the literature. Then, suddenly it was found that the Philadelphia General Hospital was reporting cases of choriomeningitis. My colleagues and I tried to determine what the new disease was. We had admitted to the Municipal Hospital 47 patients, all of whom were sent as having poliomyelitis or a condition suspected to be such. The youngest was 16 months and the oldest 26 years; 65.9 per cent were under 10 years; 55.3 per cent had a temperature of 100 F. or less. Two of the 47 patients died, and 18 were discharged with evidence of weakness or paralysis. It is interesting that three months later a check-up revealed that 2 patients had weakness or paralysis after leaving the hospital. When one sees these children alongside one another in the ward, I do not think it would be fair to say: "This child has paralysis and therefore has poliomyelitis, while this child has no paralysis and therefore has acute lymphocytic meningitis." In every case in which a patient was sent home with this syndrome the condition was diagnosed as poliomyelitis with paralysis or poliomyelitis without paralysis. It is also important to note that 4 patients were admitted with evidence of weakness and paralysis which disappeared before they left the hospital. One patient who had no evidence of weakness or paralysis on admission had it before leaving the hospital. The highest cell count of the spinal fluid was 1,280 and the lowest 14. The cells were practically all lymphocytes. We injected the spinal fluid, nasal washings and blood serum of a few patients into mice and guinea-pigs. We were unable to produce anything simulating the choriomeningitis reported. We have not yet examined histologically all the specimens. Until we find more definite evidence—from the point of view of public health—it is best to call the condition in these cases acute anterior poliomyelitis without paralysis.

There seems to be a discrepancy or dissimilarity in the clinical course in the cases presented. In Dr. Watts' cases the average duration of fever was three weeks; in Dr. Hneleski's, from ten to twelve days, and in Dr. Noone's, from three to six days. However, the spinal fluid findings were identical in all instances. In the case not included in Dr. Noone's series in which the patient died, the condition was probably poliomyelitis. It is important to study the spinal fluid in other acute noncontagious diseases. I have found in patients with serum disease, with definite evidence of rigidity of the neck, a definite lymphocytic increase in the spinal fluid. It would be interesting and a great help if more spinal fluids could be examined in other conditions than those manifested by meningeal signs.

DR. J. A. KOLMER: My interest in the virus of lymphocytic choriomeningitis refers to the possibility of its occurrence in the brain and spinal cord of Macacus rhesus monkeys, as I have employed these animals for the preparation of my vaccine for active immunization against infantile paralysis. Since the publication of the papers by Dr. Armstrong and his colleagues, it has been my custom to test the spinal cord and brain of each monkey with poliomyelitis before the cord is used in the preparation of the vaccine. It has been my custom to inoculate mice intercerebrally with 0.03 cc. of a 10 to 20 per cent suspension of the cord and brain. The mice are then kept under observation for at least twelve days, but so far I have not encountered the virus of lymphocytic choriomeningitis in

a single monkey. In this connection I may state that the monkeys are imported from India and kept under strict quarantine. Furthermore, it is my custom to permit no visitors to the animal house, in order to reduce to a minimum any chances of infection of these animals.

During the past year my poliomyelitis vaccine has been given to over 11,000 persons. Of these, about 30 per cent were children under 4 years of age; 60 per cent, children from 5 to 15 years of age, and about 10 per cent, older children and adults. To my knowledge, there have been no instances of lymphocytic choriomeningitis following the administration of the vaccine.

From the papers presented this evening I gather the impression that there is as yet no definite clinical or laboratory differentiation between lymphocytic choriomeningitis and the nonparalytic or abortive types of acute poliomyelitis; under the conditions I think it is likely that the two diseases may be readily confused. It appears, however, that the pleocytosis of the spinal fluid tends to be much higher in lymphocytic choriomeningitis than in abortive types of acute poliomyelitis. Furthermore, it appears that the pleocytosis of lymphocytic choriomeningitis is much higher than that seen in meningismus. It is interesting to learn from Dr. Armstrong that the virus of lymphocytic choriomeningitis has been demonstrated in the blood by inoculation of mice, and it is to be hoped that a practical aid in the diagnosis of the disease may be developed along these lines.

I also gather from the remarks of Dr. Armstrong that the neutralizing antibody for the virus of lymphocytic choriomeningitis may be found in the blood of recovered adults but that so far it has not been demonstrated in the blood of children. This is a perplexing situation, and I should appreciate any explanation that Dr. Armstrong may have to offer. In this connection I should also appreciate learning what percentage of serums of recovered adults has shown the presence of neutralizing antibody.

DR. ERNEST NOONE: I wish to protest mildly against generalization in discussion of the cases described at this meeting. One has no reason to believe that Dr. Watts' cases and ours represent the same entity. Neither is it surprising that differences appear in findings in adults and in children. Certainly, there were cases of poliomyelitis in Philadelphia last summer. But there is no evident reason why the disease in our cases should be classified as poliomyelitis. I too was surprised at the sequelae.

DR. CHARLES ARMSTRONG: I have been interested in all that has been said tonight. I think it has been impressed on every one that the clinical differentiation of the various conditions which may lead to the picture of aseptic meningitis is extremely difficult, if not, indeed, impossible, in many cases. My contribution consists in separating from this clinical group one definite etiologic entity, which has been designated as acute lymphocytic choriomeningitis. One should keep an open mind as to the identity of the disease in the cases encountered in Philadelphia during the past summer, as well as in Windber, Pa. Likewise, in Virginia, in the presence of a considerable number of cases of paralytic poliomyelitis, there occurred a much larger number in which no paralysis developed. According to studies by the Virginia State Department of Health, in as high as 80 per cent of the instances, or in even more in some localities, the disease was of the nonparalytic type. In a great many instances there were several cases in the same family, and in several this type of attack was suffered by persons who had previously had paralytic poliomyelitis.

I regret that our studies have caused Dr. Kolmer so much work. I do not know what Dr. Kolmer could do further in the way of practicable precautions against choriomeningitis in his monkeys. Isolation of the animals is desirable, but they might have been exposed during shipment. In this connection, Dr. J. G. Wooley has found a number of instances in which serums from merchant seamen showed the presence of immune bodies against choriomeningitis virus.

Dr. Joseph Stokes suggested that perhaps diseases of the central nervous system of this type are due in some instances to the toxins of another disease;

as a rule, when one sees lesions in virus diseases the virus also is found. Too little is known of the etiology of the postinfectious encephalitides to permit conclusions to be drawn or to generalize therefrom.

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

Joint Meeting, March 3, 1936

ISRAEL WECHSLER, M.D., *President, in the Chair*

PATHOGNOMONIC ENCEPHALOGRAPHIC SIGN OF SUBDURAL HEMATOMA. DR. CORNELIUS G. DYKE.

It is my purpose in this report to present what I consider a unique encephalographic sign of chronic subdural hematoma. Although I have encountered it only once in a series of 3,500 air studies, the fact that this unusual encephalogram occurred in 1 of 5 patients with chronic subdural hematoma on whom encephalography had been performed makes me think that it happens more often than this isolated case suggests.

Since this is primarily a roentgenographic study, only the essential features of the history and neurologic examination will be given. The patient was a man aged 43, who was admitted to the hospital on Nov. 5, 1934, and discharged on Dec. 14, 1934. He fell from a horse in 1931; a large scalp wound was sustained in the frontal region; the accident was followed by a short period of unconsciousness. About January 1934 he became somnolent, and in the following September he began to have headache, nausea and vomiting. Neurologic examination revealed unsteady gait, mild tremor of the head, slight central facial paresis on the right and blurring of the nasal margins of both optic disks.

The simple roentgenograms of the skull showed slight atrophy of the posterior clinoid processes and dorsum sellae. The pineal body was displaced inferiorly and posteriorly and slightly to the right.

On Nov. 14, 1934, encephalography was performed; none of the air entered the ventricles or cerebral subarachnoid spaces. There was a moderate amount of air in the subdural space beneath the tentorium, and its cephalic margin appeared concave anteriorly. There was a large collection of air in the subdural space over the left cerebral hemisphere; it projected diagonally in a ventral and lateral direction from the midline. Its lateral surface appeared convex superiorly and concave inferiorly in the coronal plane, but there was also a concavity superiorly and laterally in the sagittal plane. From this evidence a diagnosis of chronic left subdural hematoma was suggested.

On Nov. 19, 1934, a large, partially fluid hematoma was observed over the left hemisphere, and evacuation was performed.

The explanation of the encephalogram is: The gas (air) entered the potential space between the inner membrane of the hematoma and the arachnoid. The mass produced a concavity in the central portion of the dorsolateral margin of the sheet of air. However, at the anterior and posterior ends of the hematoma the air came in contact with the skull. The latter may give the false impression that the lateral margin of the air shadow is convex.

In summary, a case of verified chronic subdural hematoma has been described. The encephalographic findings have been set forth and explained, and it is believed that the encephalographic picture presented is characteristic of this condition.

DISCUSSION

DR. S. P. GOODHART: I saw this patient; he presented several interesting clinical features. As he had had his appendix removed, with the use of spinal

anesthesia, the anesthesia was believed to be the cause of the intense headaches, vomiting and spells of drowsiness; the drowsiness at one time increased to coma of short duration. The patient also showed a transitory palsy of the right abducens nerve which caused diplopia. The appendix showed little pathologic change. Does not this case belong to the type Dr. Wechsler described—that of abdominal pain of central nervous origin which simulates disease of the abdominal viscera? This is especially likely, as the man also had tremors suggesting extrapyramidal involvement (indirect pressure?). The difficulty in differentiating tumor and chronic subdural hematoma was considerable, as the injury dated back three years. Dr. Dyke stated that the patient was unconscious for five minutes. As I recall, the loss of consciousness was transitory, and the patient made little of it. Indeed, we considered whether the accident had any relationship to the symptoms presented. There was nothing definitely localizable in the clinical picture, and had it not been for the definiteness and assurance of Dr. Dyke concerning the diagnosis of hematoma I should have remained doubtful. As I remember, the clot was large and definitely organized. I do not see how Dr. Dyke is able, as I know he frequently is, to differentiate between air in the subarachnoid and in the subdural space. Under ordinary conditions I do not see how the air gets into the subdural space, and I should like to know how he arrives at that interpretation. I saw the patient a week ago, and he is well.

Dr. E. D. Friedman: My colleagues and I have carried out encephalography in a number of cases of subdural hematoma but have never encountered this picture. The usual picture is that of an expanding lesion in one hemisphere, with a shift of the ventricular system to the other side and complete block on the ipsilateral side. Dr. Dyke was unusually fortunate in this instance in having demonstrated a communication between the subarachnoid and the subdural space. The lumbar insufflation of air followed the avenue apparently of least resistance and reached the subdural space, permitting a beautiful demonstration of the lesion.

Dr. Cornelius G. Dyke: In reply to Dr. Goodhart's question: Subdural air forms a wide sheetlike shadow, as shown in the encephalogram in the case under discussion, while gas in the subarachnoid space passes between the gyri and produces many fine linear shadows from 2 to 4 mm. in width. Furthermore, Dr. F. J. Cramer, working at the Neurological Institute of New York, had occasion to verify the presence of gas in the subdural space after trephination.

Treatment of Obstructive Hydrocephalus by Third Ventriculostomy: Report of Two Cases. Dr. John E. Scarff.

The rational treatment of obstructive hydrocephalus demands that the cerebrospinal fluid be drained not only out of the occluded ventricular system but into a tissue space from which it can be rapidly absorbed by natural physiologic processes. Failure to observe this latter condition explains the lack of success which has followed the usual method of treating this disorder. Third ventriculostomy is the procedure which fulfils both the requirements for rational therapy named. It consists essentially of making an opening through the floor of the third ventricle directly into the subarachnoid cisternae at the base of the brain. This procedure, first described by Dandy in 1922, has received scant attention in the literature.

Two cases in which the condition was successfully treated by this method were reported.

DISCUSSION

Dr. Byron Stookey: These two cases are excellent examples of Dr. Scarff's skill. He has emphasized the essential principle of the operation and has left little for me to say. I think the operation has much more usefulness than is apparent to neurosurgeons and neurologists. Given a periaqueductal tumor, which obviously is inoperable and produces distention of the ventricular system, it is folly to attempt subtemporal decompression, for all that that accomplishes is to create a little larger space for the filling of the ventricular system and the ventricles will soon extend through the subtemporal decompression. Nor is

suboccipital decompression of any value, for the decompression is made below the level of the obstruction and, therefore, does not afford any relief. In these cases operation has heretofore been deemed impossible. The procedure described by Dr. Scarff is relatively simple and is the only decompressive procedure for relief of obstruction of the ventricular system at the aqueduct. It creates an opening through the lamina terminalis and the floor of the third ventricle into the interpeduncular cisterns, where the cerebrospinal fluid can circulate and be absorbed. The circulation of the cerebrospinal fluid is restored, and the ventricles are decompressed, even though one can do nothing for the primary lesion of the aqueduct. Patients thus relieved of intracranial pressure may live comfortably for a number of years, with great relief of the symptoms due to the hydrocephalus.

In addition to periaqueductal tumors there are other lesions in adults, such as insufficiency of the aqueduct. Aqueductal obstruction has generally been studied from the angle of total obstruction, whereas there are intermediate stages which have been termed more accurately aqueductal insufficiency. The aqueduct may have a small lumen; variations in pressure and edema may interfere with its function. From time to time patients with this condition show acute exacerbation of symptoms indicative of an obstruction. In these instances there may be an aqueductal gliosis, with aqueductal insufficiency or, as an end-stage, complete aqueductal stenosis. In such cases, this operation of puncture of the lamina terminalis is especially indicated, since an outlet for the cerebrospinal fluid can be made and circulation in the subarachnoid channels be reestablished.

In addition to its use in conditions of these two types, the operation is indicated in obstructive hydrocephalus of infants. Here one is confronted with another problem, which is one not only of obstruction of the aqueduct but, at the same time, of interference with absorption—a situation of which I have only recently been aware, since heretofore hydrocephalus of infancy has been divided into obstructive and nonobstructive types. In infants occasionally I have found a combined lesion of obstruction and defective absorption; frequently heretofore one has been unable to separate these two conditions, because there was no method of converting an obstructive into a nonobstructive lesion, thus permitting absorption. It is known embryologically that separation of the meninges does not take place until the cerebrospinal fluid begins to form. At this time the subarachnoid space develops.

I am sorry that Dr. Scarff did not show the ingenious instrument which he has devised to allow him to introduce into the third ventricle what is essentially a cystoscope, which he has modified so as to permit a complete view. The cystoscope is passed through the foramen of Munro; the floor of the third ventricle is then punctured—an operation much simpler than the one I devised. By means of this cystoscope a great deal of information will be gained.

Dr. Foster Kennedy: I have only a word to add of commendation of neurosurgeons for the development of this extraordinarily successful operation. It is twenty years since I formed a theory that in cases of tumor of the brain in which there occurred within an hour or so complete blindness, preceded by no or little diminution of vision, the condition must be due to sudden compression of the chiasm by the floor of the third ventricle. On the basis of that theory, puncture of the corpus callosum was performed with satisfactory results in 3 cases, but the difficulty after the operation was that the opening of the third ventricle through the roof was not permanent. The operation which the neurosurgeons have devised is a great improvement on puncture of the corpus callosum, and in the cases which Dr. Scarff has described, with which I am familiar, an admirable clinical result has been shown in patients that otherwise could not have been helped.

Dr. John E. Scarff: I meant to speak of puncture of the corpus callosum, when I described my cases. It is a widely used and much discussed procedure, but it is useless, for it drains the spinal fluid not into a physiologically active but into a relatively inactive subdural space, from which the fluid is difficult to remove.

I think that an impartial survey of the literature will show that little permanent success has attended punctures of the corpus callosum. It is so simple a procedure that it would be more widely acclaimed if it were successful.

ON THE SITE OF ACTION OF ACETYLCHOLINE AND ITS SIGNIFICANCE. DR. MCKEEN CATTELL and DR. HAROLD G. WOLFF.

This article appeared in *Science* (**82**:106 [Aug. 2] 1935). Reference may also be made to an article by Wolff, Cattell and Clark entitled "Liberation of Adrenergic and Cholinergic Substances in Submaxillary Gland" (*Am. J. Physiol.* **109**:375 [Aug.] 1934).

VARIETIES OF AGGRESSION IN PARENTHOOD. DR. GREGORY ZILBOORG.

A series of clinical illustrations was given, demonstrating the currents of underlying antagonism coming from the parent and directed against the child. The phenomenon is much more frequent than is commonly assumed and often breaks through, exerting a "traumatic" influence on the mental development of the child. This antagonism, hate, dislike or opposition may be conveniently covered by the single term aggression. Except in severe neuroses and psychoses its expression is seldom overt; it remains unconscious, but it does not thereby lose its dynamic force and influence. Its intensity and form depend largely on the life history and psychologic adjustment of the parents—their relationship to their own parents and siblings. A rational educational system is impossible without assessing seriously and fully this parental factor. In addition to this, it appears plausible to suspect that there are deeper factors of parental aggression which are quasi-biologic in nature, insight into and control of which is gained only with great difficulty. A further study of the unconscious emotional patterns of parental reactions is needed.

DISCUSSION

DR. SMITH ELY JELLIFFE: Of the 400,000 words in Webster's Unabridged Dictionary, approximately 18,000 may be called "trait" words, i. e., words which distinguish the behavior of one person from that of another. Dr. Zilboorg's use of the word "aggression"—the meaning that lies behind its use—is broad and inclusive of many aspects of what in essence may be termed hostile and destructive. He has given it an extended significance. Perhaps he would care to amplify the meaning of the behavior to which the term might be applied correctly far beyond that which the average thinker gives it. Thus, the criteria by which an action or attitude should be considered must reach far beyond those dealt with in the rationalizations of conscious phrasing. I think he is correct and justified in the utilization of this wider aspect of the term aggression. Similarly, and still more or less in the idiom of etymology, the meaning of the term "parental" is in need of widening.

"Words are but tokens, wise men use them as counters; they are the money of fools"—as Hobbes has remarked; so I shall not spend much more time on the meaning of the words in Dr. Zilboorg's title. I have touched on this issue because it seems to me that if one is to profit from this excellent essay the many meanings that the words parents and aggression may suggest are best brought under their more general aspects.

Dr. Zilboorg supports the thesis of environmentalism. I am in hearty agreement with him and have been for many years, not alone on important pragmatic considerations but on grounds which, while intriguingly debatable, can, I believe, be resolved technically.

I am certain that Dr. Zilboorg's environmentalism is not of the naive Rousseau type. He has shown that the child's mental apparatus—its "mind" of the schools—is not a *tabula rasa* on which the environment, and more specifically the parental environment, can write what it will. With others, he evidently holds that writings have already been there and that a mnemic inheritance—constitutional susceptibility, he called it—has already written itself into the child's organism, even before the beginning of what he has here discussed as parental influence.

I am convinced that the ancient Hebrews were not thinking of syphilis when they said that the sins of the fathers are visited on their children, "even unto the third and fourth generations." They were speaking, I believe, of the repetition compulsions of behavior patterns of which one has heard this evening and which are partial, if not complete, explanations of some of the tragedies recited. I am prepared to accept the thesis of the responsibility of those who ought to feel and know better, but I challenge the dictum and I doubt if Dr. Zilboorg would maintain it, that the complete answer is to be found on the parental side of the relationship. Nor do I feel any less lenient toward "passing the buck" to heredity. Here is an interesting situation, and one wonders if, after all, one would go far wrong if one said that the genes are the greatest of parental tyrants! I shall leave this apparent contradiction of the environmentalist situation unexpanded. Dr. Zilboorg touched on it when he said that the parent is not absolved from responsibility when the "susceptible constitution" of the child is there—whatever that may be.

A moment ago I spoke of the pragmatic advantages of the environmentalist position. In short, with a definite methodologic determinism oriented to this goal, there are pragmatic advantages which the gene methodologies do not possess. The latter offer difficulties to the environmentalist position in the explanation of pathologic conditions in twins, but here two important considerations still impede definite conclusions. Too few monozygotic twins have been reared apart, and also the fundamental position of split uniovular twins is being radically assailed. Thus, the environmentalist is pushed farther and farther into the earlier years of the aggressive situations for an adequate understanding of his position.

How far back can one go with the psychoanalytic methodology, which to date is the only worthy investigative tool one possesses, and get results which may be said to be reliable, i. e., experimentally verifiable? Here I should like to discuss certain suggestive problems of dream, play and psychotic behavior, which come from various sources bearing on the problem of tracing back into the early years, even the early months, of childhood the influences which have had determining consequences for later conduct. If the biogenetic law is valid, reconstructions in certain sensory spheres will be possible, perhaps even for intra-uterine situations methodologically. Of these last a word may be said.

I have no statistics, and female gymnasts of the circus bear few children, but I am speculatively inclined to wonder about the continuance of the tumbling propensities of circus children, just as I was (it may be remembered) some years ago regarding auditory impressions and musical activities. But I am straying from the subject of aggression, save in the sense that all sensory impressions have an aggressive aspect. They compel action in the body. The outside world of reality is the equivalent of a parental aggressor.

I do not understand why Dr. Zilboorg chose me to discuss the paper. I do not know whether he knew that I suffer from a long-standing chronic disorder. It has been in the making at least fifty years. It is called "family treeitis"—genealogic investigation. The attacks have been periodic—they come and go—some are violent and some minor, until I have reached, as in many manic-depressive states, a semidemented condition. In this investigation, I knew my great-great-grandmother. Two of my grandfathers I knew up to my tenth and twentieth years, and two of my grandmothers up to my thirties; they lived to be 93 and 96, respectively. Thus, I have known all four grandparents, and I knew all my aunts, uncles and cousins. I have five children of my own, each of whom has children; there are ten grandchildren; so I have a survey of six generations, to say nothing of the background since 1634 to 1638, when the ancestors came to Connecticut. With all this and with the ideas in which all here have been interested, I confess I have a deep sense of inadequacy in coming to any definite conclusions. Apparently, there are no fixed patterns. In the hundreds of persons whose histories are roughly charted I find no recurrences of diseases, accomplishments or sins. Psychoanalysis, however, does not work in the matter in this manner. It is not interested in the rationalizations of normal persons. It knows no such persons. It knows only persons in whom, in one way or another, situations have developed. Such persons need therapy.

Hence, one conclusion to which I must come and in which I am profoundly interested is the psychotherapeutic conclusion. Personally, I put no reliance on eugenics. Still, eugenical mechanisms work, but only over long periods—many, many years, thousands of years. I admire and have a profound respect, however, for the investigator who, hour by hour, pushes back his research into the history of the life of the child and reconstructs the outstanding events of its early life.

In conclusion, I come to something which interested me when I first read it many years ago. It is a poem by Charlotte Perkins Stetston, who practically spent her life in trying to educate the Indians. I shall give but one section of this story of "Similar Cases," as possibly applicable to the discussion of the evening.

"There was once a little animal,
No bigger than a fox,
And on five toes he scampered
Over Tertiary rocks.
They called him Eohippus,
And they called him very small,
And they thought him of no value—
When they thought of him at all;
For the lumpish Dinoceras
And Coryphodon so slow
Were the heavy aristocracy
In days of long ago.
Said the little Eohippus,
'I am going to be a horse!
And on my middle finger-nails
To run my earthly course!
I'm going to have a flowing tail!
I'm going to have a mane!
I'm going to stand fourteen hands high
On the psychozoic plain!'

"The Coryphodon was horrified,
The Dinoceras shocked;
And they chased young Eohippus,
But he skipped away and mocked.
Then they laughed enormous laughter,
And they groaned enormous groans,
And then bade young Eohippus
Go view his father's bones.
Said they, 'You always were as small
And mean as now we see,
And therefore it is evident
That you're always going to be.
What? Be a great, tall, handsome beast,
With hoofs to gallop on?
Why! You'd have to change your nature!'
Said the Loxolophodon.
They considered him disposed of,
And retired with gait serene—
That was the way they argued
In 'the early Eocene.'"

Dr. Bernard Sachs: I have been much interested in Dr. Zilboorg's paper and Dr. Jelliffe's effusion. I should like to see his genealogic tree. Considering the compliment he has paid his ancestral genes, he has turned out pretty well. I cannot say that I have heard a great deal that is new. I have heard less of drives and urges and more, a little more, about aggressions. I am afraid that Dr. Zilboorg has accentuated that term to such an extent that one will see in the

growing literature more about aggression. That word, however, does not fit the indefinite thought he had in mind. I cannot see that much has been gained by the introduction of the term—a criticism which applies to a great many other terms that have come from the same school. Possibly Dr. Zilboorg had in mind a question that has been much under discussion of late, that I myself have been interested in—the general subject of parent-child or child-parent relationship. Some cases of the terrible situations reported by Dr. Zilboorg did not impress me, and the same confusion exists in some of his inferences that is found in the inferences or deductions of many of his school. He knows which school I mean. The entire lack of logic is evident. When the boy was told to "shut up" he was silent ever after, but it cannot be proved that the fact that he was told to "shut up" was the actual cause of his being silent for the rest of his life, if he was, as I presume is true. It is a case of *post hoc* and not *propter hoc*. That is the fault of so many inferences that are drawn—the entirely illogical deductions that are made from the facts submitted.

As far as the "terrible" aggression of the parents is concerned, the trouble is that of late there has been an effort to make up for what I am willing to grant was the great mistake of former days—the excessive and severe discipline that parents imposed on children. Today, there is the other extreme that the children have been given every possible privilege, every possible right, and all rights have been denied to the parent. Recently, a long screeching headline appeared in a paper in which the word "duty" of the child toward the parent was stressed. There is no such thing as duty on the part of the child toward the parent. The word seems to give offense. One hears the old argument that it is not the fault of the child that he is brought into the world, therefore the parents are responsible for the child, and the child has no duty or obligation toward the parents. That, too, is a silly and false argument. What the parent is to the child the child will be to its own child in the years to come. Each person is nothing more than a simple, and a rather feeble, link in a long chain, and all have duties toward one another; all have obligations toward one another, so that there is no reason why any one should make such an ado about the use of the word duty in regard to the child. If one would not create such terrible bogies the parent-child relationship would be simple and would be maintained as simple. The parent has, and should have, toward the child all the natural instincts that an animal has toward its young. Above all the animal has the protective instinct, and it is proper that the parent should exercise that. In addition, the parent naturally has the right to demand that the child observe certain conditions which are necessary for its protection and its own welfare. I do not wish to go too deeply into that subject but merely to say that too much stress is laid on the great danger from parental control and that that is where I think much harm has been done. Next to the gangster film I do not know of anything—I say this deliberately—that has done more to interfere with the normal development of the child and the normal child-parent relationship than many psychoanalytic doctrines. I am willing to stand by that statement and to go into details in order to prove it. Some of the proof will be forthcoming before long. Another, absurd statement made the other day, and here I am only suggesting a few things brought out by the discussion of the "terrible" aggression of the parent, concerned a headline in a paper: "Every child born a criminal." First, there is no such thing as criminality until the child, the little animal, comes into contact with man-made laws, with conventions and traditional laws established through the ages. The child must learn to "adjust" itself to these, to use a word that is popular, but to attach the word "criminal" to a baby—and this comes from a psychiatric center in Washington—to say that every child is born a criminal, is defamation not only of the child but of the entire human race and leads to misconceptions, as so many of these terms do.

I do not know that I have said what was expected in connection with this subject of aggression, but the term was so misleading that I must confess that I found little in it to discuss and have had to touch on the parent-child relationship.

DR. RUBIN A. GERBER: I wish to ask whether Dr. Zilboorg displayed unconscious aggression, or am I displaying it in asking the question? Why was he so fearful about addressing the society in technical terms and so apologetic about using the technical terms which he did?

DR. GREGORY ZILBOORG: First, to reply to Dr. Gerber and to meet one of the objections of Dr. Sachs: I was fearful of using technical terms because words do not mean much; it does not matter what terms one uses, provided that one designates the facts empirically observed. Second, I was somewhat cautious because I noticed Dr. Sachs sitting in the front row and I once was complimented on my work by Dr. Sachs; I did not want to spoil that impression. Dr. Sachs once officially discussed a paper which I presented here, and he started his discussion by saying: "I find nothing to dispute." I shall never forget that. The remarks which Dr. Sachs has just made in connection with what I have said, as he himself stated, have nothing to do with the subject of aggression; so, without showing any disrespect to him, I shall not respond to some of them. One thing, however, should be stressed as of paramount scientific importance. The ethical, sociologic recommendations which come to the surface in the remarks of Dr. Sachs make me turn chameleon. May I become a biologist for a moment? Then I will return to my school. Biologically, when a baby is born he is given no responsibilities. One even does not wait until the baby says "wow." One just watches the time and gives him the bottle. Biologically a man is totally helpless when he is born, and for a period he remains sociologically as helpless. The child is helpless a little longer than after it learns to "wee-wee" not on the floor but in the right place; in other words, sociologic helplessness and absence of capacity for assuming duty last longer than the short time required for training in the little daily biologic duties. Biologically human beings are weaklings up to the age of 6 years; put a child of 6 in the middle of Broadway and Forty-Second Street and leave him there and see what will happen to him. Psychologically human beings are also weak, and I believe it is a sound scientific principle to insist on the duty of the parent, for the child is a biologically helpless unit; those who believe that psychologic and biologic characters are one should not invest the child with duties he cannot undertake.

Why did I choose Dr. Jelliffe to discuss my paper? He himself demonstrated that. Moreover, he once confided to me the existence of his indolent psychosis, the victim of which he has been all these years. The fundamental thing which Dr. Jelliffe pointed out was the importance of environmentalism. When he spoke of environment, he did not mean environment in its narrow sense. One is unable to change circumstances; their name is legion. One cannot change one's heredity, whether one likes it or not; as pragmatic and empirical therapists all here are interested in finding out what can be changed, what are the changeable elements. Dr. Sachs was right that so far as I said that the little boy was told to "shut-up" and did "shut-up" I did not prove that the reason that he did so was that he was told to. Of course, I did not prove it. I would have to tell the whole long story to give the proof. The question before one is simple and clear: how to study and control pathologic conditions arising from mismanagement in infancy. Dr. Sachs spoke of discipline. In order to be disciplinary one must be active; in order to be active one must act; in order to act one must have spunk; in order to have spunk one must have backbone, and in order to have all these things, one will admit, one must be aggressive. I did not invent the word, and I do not claim any responsibility for it.

Dr. Sachs' reference to gangsters and psychoanalysis is important, and I shall follow him step by step; I shall agree with him ninety-nine times out of a hundred and make a footnote that the gangster pictures are not inventions of individuals but a psychosociologic phenomenon. So is psychoanalysis, and the response of humanity to it is a psychologic phenomenon. How can one prove which is the cart and which the horse? But on the basis of Dr. Sachs' premises I think I may say that the horse is humanity and the cart at this time psychoanalysis.

DETROIT SOCIETY OF NEUROLOGY AND PSYCHIATRY

Regular Meeting, March 12, 1936

LEO H. BARTEMEIER, M.D., *Presiding*

PROBLEM OF MULTIPLE SCLEROSIS. DR. GERALD O. GRAIN.

The recognition of multiple sclerosis as a disease of considerable prevalence and unfavorable outlook establishes its importance in the field of medicine. The problem of greatest importance is that of etiology and pathogenicity. The pathologic appearances explain satisfactorily the clinical picture but provide meager material on which to formulate hypotheses. Difference of opinion still exists as to whether the pathologic changes are primarily gliomyelinic, and therefore endogenous, or primarily vascular, and therefore exogenous. A heredodegenerative etiology is no longer in favor. The work of Putnam and his associates appears to support the theory of focal demyelinization and gliosis secondary to primary thrombosis in the cerebral venules. Brickner offered the theory of the lipolytic action of enzymes in the general circulation. The theory does not satisfactorily explain the focal nature of the lesions in the disease nor the fact that certain diseases of the pancreas and liver are associated with abundance of blood lipases but not with multiple sclerosis.

Belief in a theory of specific infection seems to be gaining ground, particularly in Europe. The spirochetal theory of Kuhn and Steiner (1917) received its quietus, apparently, with the negative reports of Noguchi in 1923. Other inoculation experiments yielding suggestive bacteriologic results have been attributed to cage infections. Other theories which have failed to receive clinical or laboratory support are those of Löwenstein that multiple sclerosis is metatuberculosis, of Giraud, who demonstrated cell inclusions, of Chevassut for the rôle of *Spherula insularis*, of intestinal Monilia intoxication, of a common etiology with epidemic encephalitis and of a causal relationship with alleged neurotropic streptococci in focal infections.

When one considers that in at least 42 per cent of cases remissions of several months, even of years, are shown without treatment, one is disposed to dismiss therapeutic tests in this disease as offering support for any particular etiologic theory. Fever therapy in my hands has yielded improvement in a questionable 2 per cent of a small series of cases; others similarly have failed to support the claim of Weiss that in 65 per cent of cases in which this treatment was employed remissions of fifteen months were shown. At present, I am more favorably impressed with my results with Brickner's quinine therapy. Oral administration of liver seems of value. Spirocheticides produce only a temporary tonic effect.

SEDATIVE DRUGS. DR. T. J. HELDT.

At a time when sedative drugs play a considerable rôle not only in the competitive expression of pharmaceutic houses but in medical ministrations to patients, it may be advisable to review a few data for orientation in the classification, structure and therapeutic application of such drugs. A sedative drug to be acceptable must meet certain requirements: (1) it must have a liberal range of usefulness; (2) it must have a wide margin of safety; (3) it must have easily recognized indications of overdosage; (4) it must be free from annoying after-effects, and (5) it should mask as little as possible the symptomatology of the disease syndrome in which it is used.

When judged on the basis of their maximum action, sedative drugs in final analysis are depressor substances. Heed, then, must be given to the physiologic law which declares: All depressor substances exert a stimulating effect when used at appropriate dilution. Hence, a single sedative drug may, according to the dosage be a stimulant, a sedative (quieter) or a hypnotic (sleep producer).

It is evident, then, that considerable importance is attached to the selection of the proper drug. Of even greater importance are the patient and his reaction to the drug. In evaluating the patient and his disease, one must give attention to age, sex, weight, physical habitus, special disease processes and psychobiologic make-up.

The needs of the patient and the available drugs having in general been reviewed, it is wise to determine more specifically the problem to be met. Is it relief from pain, reduction of restlessness, production of sleep, correction of a mental state or a combination of two or more of these demands? To select from the many available drugs the one best suited to meet the problem entails a critical review. In making the selection of the proper drug, full consideration must be given to its composition and structural formula, as well as its pharmacologic action.

The apparent ease with which new analgesics and sedative drugs, some of which merit therapeutic administration, are marketed, brings a real challenge to the indispensability of the drugs derived from opium and coca leaves.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Regular Meeting, March 19, 1936

STANLEY COBB, M.D., *President, in the Chair*

USE OF BENZEDRINE IN POSTENCEPHALITIC PARKINSONISM. DR. PHILIP SOLOMON and DR. MYRON PRINZMETAL.

The effect of benzedrine sulfate was studied on 18 patients with postencephalitic parkinsonism, complaining of drowsiness, weakness and lack of energy. The dose varied from 5 to 60 mg. daily by mouth. The study was controlled by the substitution of blank pills at some time during the course of treatment in 15 cases and by the administration of benzedrine to a group of 20 patients with psychoneurosis, all of whom had symptoms similar to those of the patients with postencephalitic parkinsonism.

The results in the group of patients with postencephalitic parkinsonism were as follows: Eighteen had increase in energy; 17, disappearance of drowsiness (1 did not have this symptom); 14, decrease in muscular rigidity; 13, increase in strength, and 5, decrease in tremor (3 had no change in tremor, and 10 did not have tremor). There was disappearance of oculogyric crises in the 3 patients who had this symptom. In every instance, when blank pills were substituted beneficial effects were no longer reported, and the original symptoms returned. In the group of patients with psychoneurosis only 2 were benefited by benzedrine. Untoward effects in the total group of 38 patients occurred as follows: Twelve had insomnia; 3, restlessness and excitement; 3, dryness of the throat, and 2, anorexia, nausea and vomiting. These untoward effects occurred only during the first few days of treatment; they never proved serious and disappeared usually without the necessity of decreasing the dose of benzedrine.

It is concluded that benzedrine is a useful drug in the treatment of postencephalitic parkinsonism. It acts chiefly on the subjective symptoms and to a less extent on the rigidity and tremor.

PHYSIOLOGIC AND PSYCHOLOGIC EFFECTS OF BENZEDRINE. DR. ABRAHAM MYERSON.

Benzedrine is one of the drugs which mimic the action of the sympathetic nervous system. The studies by my colleagues and me with this drug were made on patients at the Boston State Hospital whose general physiologic reactions may be classed as normal, patients of the roentgenographic division of the Boston City Hospital, members of the laboratory staff and patients in private practice.

The presentation of the results is divided into three parts: (1) general physiologic action of the drug, (2) effect on spasm of the gastro-intestinal tract and (3) effect on mood and fatigue in normal persons and on similar states in patients with neuroses.

General Physiologic Effects.—The drug raises the pressure of the blood and spinal fluid. When it is given in doses of from 20 to 40 mg. by intramuscular injection, the blood pressure is raised after an interval of from fifteen to twenty minutes by from 20 to 50 mm. of mercury; to a less extent on oral administration. The rise lasts for from one to several hours and then recedes to normal. The reaction to continuous administration in large doses is such as to bring about resistance. After a few days the blood pressure ceases to rise in response to a dose which at first elevates it. Small doses of from 10 to 20 mg. are not associated with any rise in blood pressure. The heart rate is definitely slowed in most cases in which large doses are given. With small doses there is no effect on the heart rate. Electrocardiographic studies in a few cases showed no change from the normal. In one or two cases slight arrhythmia has been shown, but in general the heart action seems stronger and the pulse fuller after the administration of the drug. There is no effect on cyanosis. The rise in spinal fluid pressure is slight but constant.

2. The drug does not raise the blood sugar. In other words, it does not have the effect of epinephrine in this respect.

3. The drug increases the number of red and white cells considerably, although this varies in different persons. This increase is not associated with new cell formation and probably represents a squeezing of the cells from their resting places.

4. The relationship of the action of benzedrine to that of mecholin (acetyl beta-methylcholine) is shown as follows: When both the drugs are administered, the effect of the latter, that is, the effect resembling that of parasympathetic stimulation becomes dominant; the blood pressure falls; the heart rate becomes rapid, and the general effects of mecholin become conspicuous. After from fifteen to twenty minutes these effects wear off, and those of benzedrine become as manifest, or even more. If benzedrine is given first and the effect is obtained, mecholin will abolish the action for a short time, but ordinarily the benzedrine effects will outlast those of mecholin.

5. Atropine in most instances, though not in all, enhances the effect of benzedrine. This would be expected, since atropine paralyzes the parasympathetic nerve. Thus, if the blood pressure is raised by 30 or 40 mm. of mercury with benzedrine alone, it will be raised 60 or 70 mm., or even more, if $\frac{1}{50}$ grain (2 mg.) of atropine is administered simultaneously with the benzedrine. The heart rate, however, becomes markedly increased. In this particular, the effects of atropine become conspicuous, and the effect of benzedrine does not appear.

6. The relation of the action of amytal to that of benzedrine is shown as follows: Amytal given intravenously to the point of anesthesia lowers the blood pressure. If benzedrine is administered first and its effect is obtained, the blood pressure drops to about the normal for the person and does not reach the low point which it reaches with amytal alone. If amytal is administered first and the blood pressure drops, the administration of benzedrine will raise the blood pressure to about the normal level. The depth of narcosis created by amytal does not seem to be lessened, although the period of narcosis is probably shortened. The postnarcotic confusion is less marked. The lowering of the blood pressure has nothing to do with the sleep of the patient narcotized with amytal; in fact, other experiments indicate that sleep has no relationship to intracranial or somatic blood pressure. This is also evidenced by the fact that sleep is destroyed by doses of benzedrine which are without effect on blood pressure.

Effect on Gastro-Intestinal Spasm.—Roentgenographic studies were made by Dr. Max Ritvo on a series of over 200 persons in the roentgenographic service of the Boston City Hospital and, on several occasions, on patients in private practice. If spasm is shown to be present, whether due to functional

disturbance or disease of organs other than the stomach and intestines, such as the gallbladder, or associated with ulcer or cancer of the gastro-intestinal tract, it is promptly and efficiently relieved by the oral administration of from 20 to 30 mg., in certain cases 40 mg., of benzedrine. In such cases, the roentgenograms are markedly improved; organic lesions are more sharply outlined and more readily differentiated; functional spasm disappears, and the general roentgenographic situation is improved. In cases of spasm of the colon the drug works remarkably well. There are no side-effects; peristalsis is not disturbed to any noticeable extent, and the filling time is on the whole improved because of the relaxation of spasm. In general, the drug seems ideal for roentgenographic purposes and is of definite clinical importance in the relief of abnormal spasticity.

Effect on Mood and Fatigue.—Presumably, there is a central effect from the administration of small doses of benzedrine which is not associated with any changes in blood pressure or action on the heart and which may be summarized as follows:

1. In the normal person who suffers from temporary fatigue and depression due to disturbance in sleep or worry, from 10 to 20 mg. of benzedrine taken on arising and at noon acts efficiently and pleasantly. This is probably only an emergency measure. It has not been used continuously in normal persons. There are no bad effects if the drug is taken in the early part of the day and in moderation. In larger doses, and especially if taken in the late afternoon, it disturbs sleep and may even create a "jittery" state.

2. In certain neuroses in which there are fatigue and depression in the morning and the symptoms tend to disappear toward the middle of the day, from 10 to 20 mg. of benzedrine, or a dose administered with regard to individual idiosyncrasy, is often of great help. It is not curative but is definitely ameliorative. The pleasantness of the effect is constantly commented on. The only side-effect which we have noticed is the slight interference with appetite of which some patients complain. This is probably due to interference with the tonus of the gastro-intestinal tract.

3. Many patients with neuroses are not helped. It is probable that the status of the autonomic-pharmacologic balance is an important matter to establish before the administration of this or any sympathetic or parasympathetic drug.

DISCUSSION

DR. MAX RITVO: Benzedrine has been proved of great value in abolishing spasm of the stomach and intestines. Spasm is a troublesome factor in the roentgen examination of the gastro-intestinal tract, because spastic manifestations may closely simulate organic lesions or may obscure underlying pathologic processes and lead to an incorrect conclusion. In some instances the spasm may persist for long periods, and it may be impossible to determine whether the spastic contracture is purely functional or is associated with an organic lesion. Roentgenologists have resorted to atropine, massage of the abdomen, reassurance of the patient and other measures in an effort to abolish spasm. None of these measures is uniformly successful. With the use of physostigmine it is possible so to increase peristaltic activity that the stomach contents may be forced through the pylorus and duodenum, in spite of any spastic contracture which may be present; however, the action of physostigmine increases the spasm, and this may be objectionable in some instances.

With benzedrine sulfate administered orally, it is possible to abolish spasm of the stomach and pyloric sphincter in a high percentage of cases. The effect is usually obtained in from ten to fifteen minutes, and there need be no interference with the routine roentgenographic studies of the gastro-intestinal tract. The drug does not cause unpleasant side-effects or other serious complications. The blood pressure is usually elevated by the administration of benzedrine, and caution is recommended in its use in patients with hypertension or severe heart disease. This drug has a definite place in the roentgen examination of the gastro-intestinal tract and will doubtless prove of great aid to the roentgenologist.

DR. W. N. HUGHES, Providence, R. I.: I shall make a few remarks not about benzedrine and epidemic (lethargic) encephalitis but about the use of ephedrine in the treatment of Parkinson's syndrome associated with paralysis agitans. The few patients I have treated with ephedrine have shown improvement in strength and speech, as have the persons treated with benzedrine in the cases reported. My patients were given scopolamine hydrobromide and at times stramonium, and perhaps the effect from the ephedrine was greater because of this than it otherwise would have been. One patient had great difficulty in starting the flow of urine until the dose was cut down. One patient was well in the daytime, but the dose had to be stopped, as there developed incontinence at night. Increased muscular contraction, which occurred with ephedrine during the day, disappeared, and then more marked relaxation occurred, so that the patient become incontinent in the evening. Speech improved considerably in this patient. I saw this afternoon a patient whom I had seen five weeks before with vasomotor rhinitis. She was given 10 mg. of benzedrine daily in the early morning and obtained great relief.

DR. W. BLOOMBERG: The group of 9 patients with narcolepsy, the original persons to whom benzedrine was administered, has grown to 35. Complete relief has been obtained with benzedrine in every case. I have used benzedrine with scopolamine in cases of parkinsonism, with much relief. One patient in a catatonic stupor to whom benzedrine was administered responded to stimuli somewhat better than before the drug was given.

DR. STANLEY COBB: This warning should be sounded: Benzedrine is available in all drug stores. There is no telling where this will lead; a drug that will keep one awake is enticing and may be harmful.

DR. J. LOMAN: Benzedrine does not affect the depth of narcosis, but it shortens the period.

DR. A. MYERSON: We have taken into account the matter of habituation. One patient, whom we have treated for a long time, has been ill for thirty years. During this period he has awakened each morning with a wish for death; that this is no idle matter is evidenced by the fact that three relatives have committed suicide. Daily administration of 40 mg. of benzedrine during the eight months of treatment has had a good effect. The amount taken varies according to the feeling of depression when he awakens. That benzedrine is not habit forming is due to the fact that it does not leave the patient at a lower level when the effects wear off. A drug is habit forming because when the effects wear off the patient feels worse than when he took it and consequently needs constantly increasing doses to bring about the same effect. We give benzedrine in small doses and have not seen any evidence of habituation.

FUNCTIONAL DETERMINANTS OF CEREBRAL LOCALIZATION. DR. K. S. LASHLEY.

This paper will be published in full in a later issue.

Book Reviews

Aphasia: A Clinical and Psychological Study. By Theodore Weisenburg, M.D., and Katharine E. McBride, Ph.D. Cloth. Price, $5. Pp. 634. New York: Commonwealth Fund, 1935.

This book, published after the death of Dr. Weisenburg, is a fitting monument to his life's work. The aphasias are not only a clinical subject for study but a much trampled debating ground in which claims conflict with counter claims and tempers clash. It is an eloquent tribute to the wisdom and maturity of the senior author that rival views are discussed, criticized, exposed and rejected and that, nevertheless, polemic is avoided. The approach is as objective and critical as the complexity of the subject permits. Three hundred and fourteen cases were investigated; of these, 234 were studied, and in 60 the patients were examined with astounding intensity, both as to clinical symptomatology and as to psychologic responses. Previous studies by numerous observers have suffered from various shortcomings: Neither the clinical nor the psychologic examinations were sufficiently standardized; control series, both of "normal" subjects and of patients with unilateral cerebral lesions not associated with aphasia, were missing, and when standardized tests were employed their validity and reliability were not determined. Moreover, practically every comprehensive investigation into the subject of the aphasias was dominated by dogmatic hypotheses which had to be demonstrated and "proved." Weisenburg has either eliminated these faults or reduced them to the inevitable minimum. It is particularly the inclusion of control groups in the form of 85 "normal adults" and 38 patients with unilateral cerebral lesions not associated with aphasia that renders the study so valuable from the point of view of objectivity and comparability.

Head and Marie strove for something new and original and, in a sense, achieved their ends. But the originality was obtained at the expense of systematic thoroughness. Weisenburg exercised wise restraint in the quest for originality but spared no labor to be thorough and systematic. Accordingly, he furnished nothing essentially new but supplemented the old available material with such an abundance of controlled observations that his results acquire the value of confirmatory evidence. Chapters 15, 16 and 17 give an almost day by day account of the "course of aphasic disorders," "reeducation in aphasia" and "the psychological changes in aphasia," which in thoroughness and systematic procedure outweighs everything thus far produced in the field. The chapters are a wholesome demonstration of the superiority of methodical persistence over ingenious generalization.

There is hardly anything missing in this book that can reasonably be expected in a treatise on the aphasias. Symptomatology is ably covered, and the separate syndromes, including the apraxias and agnosias, are discussed in such lucid form that the work could well be used as a textbook for beginners. Classification is approached in a spirit of humility and sound compromise. Four groups are elaborated: (1) the predominantly expressive, (2) the predominantly receptive, (3) the expressive-receptive and (4) the amnesic. The various groups are well described and amply illustrated by well chosen case histories.

The various schools of thought that helped to shape present concepts of the aphasias are discussed and critically evaluated. The discussion is remarkable for its sense of fairness. None of the views, whether they are postulates of strict localization or beliefs in the "equipotentiality of the cortex," is discarded. The kernel of truth that is contained in each is retained, and the final conclusions are reached that "no single hypothesis will account for the changes" and that "the individual differences" must dictate the process of examination and study.

The scarcity of pathologic studies is an undeniable defect. Three necropsies only were obtained in the course of the investigation. Accordingly, the authors

refrain from hasty deductions in the matter of localization and content themselves with restating the problem from previously acquired personal knowledge and from generally known facts.

On the basis of the psychologic tests and clinical examinations the authors conclude that "aphasia is a particular deterioration, not a general intellectual defect."

It is impossible to do justice to the wealth of material that is not merely accumulated but painstakingly elaborated in this volume. A full appreciation of the accomplishment can be gained only from reading both the theoretical parts and the descriptions of the cases, with the detailed reports of tests, charts and tables. The style is fluent and the presentation readily intelligible. The book can be safely recommended both to the special worker in the field, to whom it will give a synopsis of the subject, and to the general practitioner, whom it will supply with an easily understood exposition of the problems involved.

Tentatives opératoires dans le traitement de certaines psychoses. By Egas Moniz. Price, 40 francs. Pp. 248, with 39 illustrations. Paris: Masson & Cie, 1936.

This book reports a detailed study of twenty patients on whom Moniz performed partial destruction of the white matter of the prefrontal area on both sides. Its importance can scarcely be overestimated, and one will wait impatiently for time to elapse, so that a follow-up report can be made on the eventual outcome. Certainly, the immediate results (the operations were performed late in 1935 and early in 1936) are striking. Moniz based his experiments on the theory that in certain so-called functional psychoses there is fixation of certain patterns of relationship among various groups of cells. The cell bodies may remain normal and their processes show no anatomic alterations, but their multiple connections, variable in normal persons, may develop more or less fixed arrangements, which may lie at the bottom of the persistent ideas and delusions characteristic of certain morbid psychic states.

The operations consisted in the injection of absolute alcohol or in cutting spheroids with a leukotome within the white matter of the frontal lobe anterior to the premotor region on both sides in such a way as to destroy to a greater or less extent the connection of the frontal pole with the rest of the brain. No patient died, and none was made worse by the operation.

The patients subjected to the operation were mostly disturbed and suffered from depression, anxiety, delusions or hypomania with irritability and assaultiveness. Most of them had been in a hospital for a long time. The best results were obtained in cases of agitated depression, four of five patients making a social recovery; of the seven patients with schizophrenia, only two were improved. In many instances there was persistence of the underlying thought processes but subsidence of the pressure and affective state, so that the patients gave voice to delusions without insistence and almost as though they realized that they might have been mistaken. Six weeks after operation Moniz found seven patients who had recovered, seven who had improved and six whose condition was changed. From reading the detailed protocols this seems a conservative estimate.

The deficit symptoms of destruction of the frontal lobe were in evidence immediately after operation but tended to subside with lapse of time; no case is reported in which there was any persistent disturbance of memory or intelligence. Some apathy, disorientation, mutism and negativism, loss of initiative and disturbances of the sphincters and pupils were noted in almost all cases; however, they were transitory, persisting longest in cases in which the most extensive operations had been performed. Incidentally, in some instances operation appears to have been incomplete; further gratifying results may appear subsequent to more complete blocking of the prefrontal areas.

While the implications of this work are greatest for the psychiatrist, the volume cannot fail to interest also the psychologist, the neurophysiologist and the neurologist. It is to be hoped that a translation of this work will bring it before a wider circle of readers.

Extra-Ocular Muscles. By Luther C. Peter, A.M., M.D., Sc.D., Professor of Diseases of the Eye in the Graduate School of Medicine of the University of Pennsylvania. Second edition. Price, $4.50. Pp. 343, with 136 engravings and 5 colored plates. Philadelphia: Lea & Febiger, 1936.

The book is well written, arranged and edited. Facts are clearly stated and readily understandable. The book is rich in practical illustrations. Many methods of examination and instruments of precision are described. The author's vast experience enhances the worth of the personal opinions expressed regarding the evaluation of the various instruments. The part on surgical technic is a valuable addition to the book. A representative group of operations are clearly and concisely described, and in general the reasons for the author's choice of operation are well founded. In this respect he is conservative, fair and broad minded. Occasionally he lapses into the rôle of one lecturing to medical students. Less reiteration would also be desirable. The book is not an exhaustive discussion, yet it is of proper length. It fulfils the author's purpose and is a worth while addition to the subject.

Das supra-Vestibuläre System bei den Tieren und beim Menschen, mit besonderer Berücksichtigung der Klinik der Blicklähmungen, der sogen. Stirnhirnataxie, der Zwangsstellungen und der Zwangsbewegungen. By Dr. L. J. J. Muskens. Price, 15 guilder. Pp. 557, with 48 illustrations. Amsterdam, the Netherlands: N. V. Noord-Hollandsche Uitgevers maatschappij, 1934.

This large volume deals with forced movements from the anatomic, physiologic and clinical points of view. The author elaborates his conception of the supravestibular system, including the nucleus of the posterior commissure and the nucleus interstitialis, and the significance of this system for the movements of the body and eyes.

THE AMERICAN ORTHOPSYCHIATRIC ASSOCIATION

The fourteenth annual meeting of the American Orthopsychiatric Association will be held at the Roosevelt Hotel in New York, Feb. 18, 19 and 20, 1937. The president of the society is Dr. Edgar A. Doll, and the secretary, Dr. George S. Stevenson, 50 West Fiftieth Street, New York.

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